MULTIMORBIDITY AND MEDICATION MANAGEMENT IN GENERAL PRACTICE; A CHALLENGE FOR GPS

JUDITH SINNIGE

MULTIMORBIDITY AND MEDICATION MANAGEMENT IN GENERAL PRACTICE;

a challenge for GPs

Judith Sinnige

The research presented in this thesis was conducted at the Scientific Institute for Quality of Healthcare (IQ Healthcare), and the Netherlands institute for health services research (NIVEL). IQ Healthcare is part of the Radboud Institute for Health Sciences (RIHS), one of the approved research institutes of the Radboud university medical center, Nijmegen.

Cover : Roel ter Voort, Voorts
Lay-out: Judith Sinnige
Print: ProefschriftMaken
ISBN: 978-94-6295-715-2

MULTIMORBIDITY AND MEDICATION MANAGEMENT IN GENERAL PRACTICE; a challenge for GPs

Proefschrift
ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op
dinsdag 31 oktober 2017
om 14.30 uur precies

door
Elisabeth Johanna Sinnige
geboren op 3 oktober 1986
te Beverwijk

Promotoren:	Prof. dr. G.P. Westert Prof. dr. F.G. Schellevis (VU Medisch Centrum)
Copromotoren:	Dr. J.C.C. Braspenning Dr. ir. J.C. Korevaar (NIVEL, Utrecht)
Manuscriptcommissie:	Prof. dr. M.G.M. Olde Rikkert Prof. dr. W.J.J. Assendelft Prof. dr. R.J. van Marum (VU Medisch Centrum)

CONTENTS

Chapter 1

General introduction

GENERAL INTRODUCTION

Primary health care is characterized by providing general medicine, by its person-centered and integrative approach to the patient and by the principle of continuity of care[1, 2]. The general practitioner (GP) -or family physician or family doctor- therefore, sees patients from all ages with a broad range of health problems and health conditions. Due to the aging population[3], which is the consequence of an increase in life expectancy, and a decrease in mortality by improvements in medical care, the patient population in a general practice becomes relatively older. A substantial part of these older patients visits the practice for management of one or -more likely -, *multiple* chronic diseases, like diabetes mellitus, chronic obstructive pulmonary disease (COPD) or osteoarthritis. Having multiple chronic diseases impedes daily life for these patients; they experience a lower quality of life, functional limitations, psychosocial problems, and they have higher rates of health care utilization[4-10]. As a consequence, the presence of multiple chronic diseases introduces many challenges for the GP. Management of this specific patient group often means the prescription of multiple medications, so one of the GP's major challenges concerns medication management. This thesis focuses on the prevalence of patterns of chronic diseases in general practice, as well as the complexity of medication management in older patients with multiple chronic diseases.

Prevalence and patterns of multimorbidity

The presence of multiple (chronic) diseases within one person is known as *multimorbidity*. This concept was first introduced by Van den Akker and colleagues in 1996[11], and was derived from Feinstein's original definition of *comorbidity* which was described as *'any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index-disease under study'*[12]. Multimorbidity can be distinguished from comorbidity by the fact that it does not include a specific index-disease (e.g. an asthmatic patient with co-occurring heart failure and osteoarthritis), see **Figure 1.**

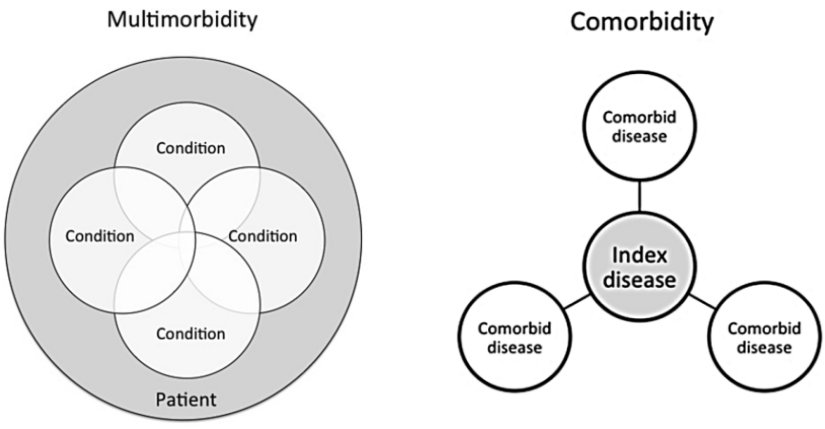


Figure 1: Schematic overview of the concepts multimorbidity and comorbidity (Boyd & Fortin, 2010)[13].

As of the unprecedented increase in chronic degenerative disorders in society, research in the field of multimorbidity has received increasing attention over the last few decades. The relevance of these studies is underlined by the generally high prevalence rates of multimorbidity. However, since the definition of multimorbidity is operationalized differently in prevalence studies[14-18], this has led to a considerable range in assessed prevalence rates of multimorbidity; from around 20-30% in persons from all ages, to 55-98% when focusing on persons aged 60 years and older[14, 19]. Next to differences in defining multimorbidity, research outcomes on multimorbidity vary due to differences in the chosen study population (e.g. general population vs. chronically ill population), the healthcare setting (e.g. general practice setting vs. ambulatory care setting), or data source (e.g. medical record data vs. survey data)[20]. Thus, as a result of the heterogeneity in the measurement of multimorbidity there remains uncertainty about the precise extent of multimorbidity in general practice.

In everyday practice, GPs respond on patients' reason for encounter by taking into account their additional prevalent problems and diseases. They manage a patient with a specific combination of diseases instead of a multimorbid patient itself. Information about the prevalence of *multimorbidity patterns* seems therefore particularly relevant for GPs. For instance because they would be able to anticipate on certain diseases which turn out to be more likely to occur in a certain multimorbidity pattern. Available studies on this topic either focused solely on disease pairs -which might not reflect the true situation as older patients often have more than two diseases[21, 22]-, or reported very broad -not practically manageable- disease patterns[23, 24]. Thus, practical evidence on manageable and realistic multimorbidity patterns is still lacking.

Multimorbidity and polypharmacy

Patients with multimorbidity commonly use several medications simultaneously, which is also referred to as *polypharmacy.* Often, polypharmacy is defined as the chronic use of at least five different medications[25-27]. An Italian study found that around 46% of a primary care population aged 65 years and over received five different medications in 2005[25], and there is evidence that the prevalence of polypharmacy has increased in the last decennium[27]. Older patients using several medications are at increased risk for (potentially) inappropriate prescribing. This refers to the use of medications that should be avoided, and doses or frequencies of medications that should not be exceeded[28, 29]. Besides the increased risk for inappropriate prescribing, polypharmacy is associated with poor medication adherence, an increased risk for adverse drug events, and unplanned hospitalizations[26, 30]. Thus, attention for appropriate management and medication prescribing is essential.

Management of older patients with multimorbidity and polypharmacy

Management of older patients with multimorbidity and polypharmacy, like their medication management is not that simple or apparent for GPs[31-33]. In general, the structure of the current health care system hinders GPs to adequately manage older patients with multimorbidity. For instance, GPs experience a lack of time during a regular (10-minute) consultation to adequately manage the problems of patients with multimorbidity, and this high workload is also perceived by patients[34-36]. Further, fragmentation and poor coordination of care is not uncommon since patients with multimorbidity are often seen by several health care providers, working both in primary as well as in secondary care[32, 37-40]. In addition, health care providers experience poor inter-professional communication, for instance between GPs and medical specialists, or between GPs and pharmacists[34, 41, 42]. The disease-centered approach characterizing the current health care system also complicates management of patients with multimorbidity and polypharmacy[43-45]. This approach means that traditionally, medical care is focused on the prevention, diagnosis, and treatment of *single* diseases, and that the accompanying clinical practice guidelines (CPGs) are centered around a single condition[46]. GPs are encouraged to adhere to these CPGs, which have been developed in all areas of medicine as a means to improve quality of care[47, 48]. However, in every day practice -where multimorbidity is common-, the question rises whether and to what extent these guidelines support multimorbidity management[31-33, 49-51]. Prescribing medications according to recommendations in CPGs may result in an excessive amount of medications with the increased risk for drug interactions, poor adherence and adverse effects[26]. To illustrate, when adhering to the CPGs a 79-years old patient with Diabetes Mellitus type 2, COPD, osteoporosis, osteoarthritis, and hypertension was recommended to take twelve different medications in nineteen doses per day, on five different moments of the day[31]. GPs therefore, often balance between adhering to the available disease-specific CPGs and providing patient-centered care[31, 33, 45, 49, 52]. Above all, in this older patient group other considerations can become complementary or even superior to medical motives, for instance patients' quality of life, their preferences or their expectations. Due to a lack in guidance and the patient-specific circumstances, it is challenging to convert these factors into appropriate medical practice[32, 37, 39].

Variation in medication prescribing between physicians

In older patients with multimorbidity and polypharmacy, periodic adjustment of the prescribed medications is necessary, because of regular changes in conditions of life and treatment effects. Due to the fact that it is not always possible to adopt the recommendations on medication prescribing stated in the single-disease CPGs, GPs sometimes experience a lack of confidence or clinical competence to manage older patients with multimorbidity adequately; there seems to be clinical uncertainty[34, 41]. For instance, at moment when deliberating on stopping a prescribed medication. Moreover, a logical result of the limited applicability of practice guidelines, the availability

of multiple treatment options, and the influence of the physician and patient themselves on the treatment, is *variation in medical practice between physicians*. Variation in the (number of) prescribed medications to patients with similar characteristics is not necessarily worrisome if it is justified. GPs often have grounded reasons for adding -or not- a subsequent medication to a patient who already uses several medications[39, 41]. In order to elucidate the 'not-rational' part of medication prescribing variation, a better understanding of the rational part of medication prescribing variation is needed. Furthermore, little is known on how GPs assess the benefits and harms of available treatment options and by what kind of factors medication management is influenced. So, evidence is lacking or inconclusive on the process of medication management for this patient group in general practice[43].

Decision making tools for medication management in general practice

Despite the increasing prevalence of multimorbidity and the challenges it provides for care providers, only a few effective interventions to improve outcomes for patients with multimorbidity exist, with only three focusing specifically on medication management[53, 54]. Tools or support centered around medication management of patients with multimorbidity seem urgent, and for providing optimal pharmaceutical care in this patient group inter-professional collaboration is desired, by involvement of pharmacists. An effective method to improve or strengthen medication prescribing, involving several health care professionals, is to give audit and feedback[55]. Feedback and audit appears to be most effective when provided regularly by a colleague health professional or supervisor, and efficient prescribing and dispensing of medications is most efficient when audit meetings have strict rules around medication choices[56-58]. In the Netherlands, these audit meetings (in Dutch: FTO) are increasingly organized, however, there is variation in the organization level and frequency of these meetings[57]. Computer decision support systems incorporated in GPs' and pharmacists' electronic health record system have proven to reduce the use of potentially inappropriate medications[59, 60], but there is the problem of ignoring the (many) medication prescribing alerts the system gives[59]. Screening tools can also assist GPs and pharmacists in the process of identifying potentially inappropriate prescribing and prescribing omissions. Examples are the Medication Appropriate Index[61], the Beers' criteria[62], and the more European focused STOPP/START-criteria[63, 64]. The STOPP/START-criteria were also incorporated in the Dutch multidisciplinary guideline on polypharmacy, which is focused on the performance of *clinical medication reviews* (CMR) among the elderly[65, 66]. A CMR is a '*critical examination of a patient's medications -involving the patient, GP and pharmacist-, with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medications, minimizing the number of medication related problems and reducing waste*'[67]. Performing CMRs have positive effects on the number of drug related problems, patient satisfaction with the medications, and medication adherence. However, conclusive positive effects of CMRs on

clinical outcomes such as reduced hospital admissions or mortality rates are still lacking[68-71]. Furthermore, more practically, it still seems hard to select patients eligible for a review based on the available patient information recorded in pharmacists' and GPs' electronic health record systems[72, 73]. So, there is still room for improvement in the process of performing CMRs in older patients with polypharmacy, as well as in studies on effectiveness of CMRs on patient outcomes. In sum, tools and decision aids on management or medication prescribing are available. Yet, positive effects of these tools are inconclusive, there are practical problems or there is few evidence of the use or implementation of these tools in daily practice.

Research objective and research questions:

The aim of this thesis is to identify and clarify the challenges and complexity of managing older patients with multimorbidity in general practice, with a special focus on medication management. Expanding our knowledge as regards these facets can contribute to new insights for practice and scientists in the fields of multimorbidity and polypharmacy, and can improve patient's health care.

With this specific objective in mind, the following research questions were formulated, focused on older patients in general practice:

1. In an international perspective, which disease combinations are most prevalent?
2. What is the multimorbidity rate in patients with common chronic diseases in the Netherlands, and what kind of multimorbidity patterns occur in older patients with specific chronic diseases?
3. What is the variation between general practices in polypharmacy rates of older patients?
4. What is the GP's medication management strategy for patients with multimorbidity and polypharmacy?
5. What is the target group eligible for a medication review, from the GP's and pharmacist's perspective, and what are practical barriers and facilitators for performing a medication review?

Outline of this thesis:

Chapter 2 covers research question one and describes the prevalence rates of disease combinations found in the literature, and the methodological issues related to determine prevalence rates of disease combinations. *Chapter 3* covers research questions two and examines the prevalence of multimorbidity patterns in an older primary care population (aged 55 years and over) by using electronic health record data of GPs within a 10-year period. *Chapter 4* covers research question three and focuses on polypharmacy among older patients, and the variation of polypharmacy prevalence rates between general

practices by combining general practice data and pharmacy data. In *chapter 5* research question four is answered and explores the views of GPs on medication management in older patients with multimorbidity and polypharmacy. *Chapter 6* covers research question five and describes the practical organization of medication reviews in older patients and it explores the potential target group for a medication review by comparing the views of GPs and pharmacists with criteria for identifying patients potentially in need for a medication review. This thesis closes with a summary and general discussion of the main findings and provides recommendations for practice and research, which are presented in *chapter 7* and in *chapter 8.*

General practice care in the Netherlands

In the Netherlands all inhabitants are obligatory insured for a basic health care insurance package that includes -among others-, care provided by the GP. Costs for treatment that are not covered within the basic package can be reimbursed via a supplementary voluntary health insurance. No payment is required for consulting a GP in the Netherlands. All inhabitants are listed in a general practice, but they are free to select their GP of choice; usually they choose a GP from a practice located in their own neighborhood. Similar to countries like Norway, the United Kingdom and Italy, a full gatekeeping system is in place in the Netherlands. This means that patients are required to have a referral from their GP for access to most medical specialists[74, 75]. In general practice care, patient records are considered vital as they comprise all information that is essential to provide adequate medical care. To date, virtually all GPs in the Netherlands use an electronic medical record system to register the relevant medical information of their patients who consult them. A favorable effect of the gatekeepers role of the GP is that electronic medical record data of general practices are most likely to be a complete source of information related to patients' chronic conditions, prescriptions and referrals[76]. Practices differ in size and in the different professions involved in the practice team. Small practices will consist of only one GP with a practice assistant, while larger practices include several GPs, supporting (specialized) nursing staff, and additional professions. A small part of the practices are also licensed to dispense medication prescriptions. In the Netherlands in 2014, 22% of the practices were considered single-handed practices, while 40% and 39% considered duo- and group practices, respectively[77]. Of all registered Dutch patients, 76% contacted a GP in 2014, with an average of four consultations per patient per year. The average consultation rate was 13 for patients aged 85 years and older. Most often, patients consulted the GP for problems related to the musculoskeletal system, the skin, and the respiratory system[78]. When medications are prescribed by the GP, they are usually dispensed by a pharmacist in a community pharmacy (i.e. a pharmacy that carries a stock of medications for dispensing and is open to the public). Around 60% of the patients between 18 and 64 years received at least one medication prescription in 2014. For patients 65 years and older this was 90%[78]. The most frequently prescribed medication was a proton-pump-inhibitor, a group of drugs that reduces gastric acid production; on average 15% of the patients received a prescription. Additional frequently prescribed medications were non-steroidal inflammatory drugs (NSAID) and antibiotics[78].

References:

1. Landelijke Huisartsen Vereniging LHV, Nederlands Huisartsengenootschap NHG. Toekomstvisie huisartsenzorg. Modernisering naar menselijke maat; Huisartsenzorg in 2022. [http://www.tkv2022.nl/]
2. Zaat J: Terug naar Woudschoten. *Huisarts en Wetenschap*. 2001;44(5):547-548.
3. UN Department of Economic and Social Affairs Population Division. World Population Ageing 2013. New York. 2013.
4. Jansen D, Spreeuwenberg P, Heijmans M. Ontwikkelingen in de zorg voor chronisch zieken: rapportage 2012. Utrecht: *NIVEL*, 2012.
5. Fortin M, Bravo G, Hudon C, Lapointe L, Almirall J, Dubois MF, et al. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res.* 2006;15(1):83-91.
6. Kadam UT, Croft PR, North Staffordshire GPCG. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. *Fam Pract.* 2007;24(5):412-419.
7. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract.* 2011;61(582):e12-e21.
8. Tinetti ME, McAvay GJ, Chang SS, Newman AB, Fitzpatrick AL, Fried TR, et al. Contribution of multiple chronic conditions to universal health outcomes. *J Am Geriatr Soc.* 2011;59(9):1686-1691.
9. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162(20):2269-2276.
10. Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M, et al. Review: health care utilization and costs of elderly persons with multiple chronic conditions. *Med Care Res Rev.* 2011;68(4):387-420.
11. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. *Eur J Gen Pract.* 1996;2:65-70.
12. Feinstein AR. The pre-therapeutic classification of comorbidity in chronic disease. *J Chron Dis.* 1970;23:455-468.
13. Boyd CM, Fortin M. Future of multimorbidity research: How should understanding of multimorbidity inform health system design? *Public Health Rev.* 2010;32:451-474.
14. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann Fam Med.* 2012;10(2):142-151.
15. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multi-morbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Ann Fam Med.* 2012;10(2):134-141.
16. De Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol.* 2003;56(3):221-229.
17. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases- A systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci.* 2011;66A(3):301-311.

18. Van den Akker M, Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. *J Clin Epidemiol.* 2001;54(7):675-679.
19. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: A systematic review of the literature. *Ageing Res Rev.* 2011;10(4):430-439.
20. Schram MT, Frijters D, van de Lisdonk EH, Ploemacher J, de Craen AJ, de Waal MW, et al. Setting and registry characteristics affect the prevalence and nature of multimorbidity in the elderly. *J Clin Epidemiol.* 2008;61(11):1104-1112.
21. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* 2012;380:37-43.
22. Marengoni A, Rizzuto D, Wang HX, Winblad B, Fratiglioni L. Patterns of chronic multimorbidity in the elderly population. *J Am Geriatr Soc.* 2009;57(2):225-230.
23. Holden L, Scuffham PA, Hilton MF, Muspratt A, Ng SK, Whiteford HA. Patterns of multimorbidity in working Australians. *Popul Health Metr.* 2011;9(1):15.
24. Schafer I, von Leitner EC, Schon G, Koller D, Hansen H, Kolonko T, et al. Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions. *PLoS One.* 2010;5(12):e15941.
25. Nobili A, Franchi C, Pasina L, Tettamanti M, Baviera M, Monesi L, et al. Drug utilization and polypharmacy in an Italian elderly population: the EPIFARM-Elderly Project. *Pharmacoepidemiol Drug Saf.* 2011;20(5):488-496.
26. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother.* 2007;5(4):345-351.
27. Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. *BMC Clin Pharmacol.* 2010;10:16.
28. Milton JC, Hill-Smith I, Jackson SH. Prescribing for older people. *BMJ.* 2008;336(7644):606-609.
29. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. *J Clin Pharm Ther.* 2007;32(2):113-121.
30. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet.* 2007;370(9582):173-184.
31. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA.* 2005;294(6):716-724.
32. Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med.* 2011;171(1):75-80.
33. Tinetti ME, Bogardus ST, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med.* 2004;351:2870-2874.
34. Smith SM, O'Kelly S, O'Dowd T. GPs' and pharmacists' experiences of managing multimorbidity: a 'Pandora's box'. *Br J Gen Pract.* 2010;60(576):285-294.
35. Fried TR, Tinetti ME, Iannone L. Primary care clinicans' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med.* 2011;171(1):75-80.
36. Noel PH, Frueh BC, Larme AC, Pugh JA. Collaborative care needs and preferences of primary care patients with multimorbidity. *Health expect.* 2005, 8(1):54-63.

37. Luijks HD, Loeffen MJ, Lagro-Janssen AL, van Weel C, Lucassen PL, Schermer TR. GPs' considerations in multimorbidity management: a qualitative study. *Br J Gen Pract.* 2012;62(600):e503-510.
38. Bodenheimer T. Coordinating care--a perilous journey through the health care system. *N Engl J Med.* 2008;358(10):1064-1071.
39. Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC Fam Pract.* 2012;13:56.
40. Bayliss EA, Edwards AE, Steiner JF, Main DS. Processes of care desired by elderly patients with multimorbidities. *Fam Pract.* 2008;25(4):287-293.
41. Moen J, Norrgard S, Antonov K, Nilsson JL, Ring L. GPs' perceptions of multiple-medicine use in older patients. *J Eval Clin Pract.* 2010;16(1):69-75.
42. Maeng DD, Martsolf GR, Scanlon DP, Christianson JB. Care coordination for the chronically ill: understanding the patient's perspective. *Health Serv Res.* 2012;47(5):1960-1979.
43. American geriatrics society expert panel on the care of older adults with multimorbidity. Guiding principles for the care of older adults with multimorbidity: An approach for clinicians. *J Am Geriatr Soc.* 2012;60:E1-E25.
44. Guthrie B, Payne K, Alderson P, McMurdo MET, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. *BMJ.* 2012;345:e6341.
45. Fortin M, Contant E, Savard C, Hudon C, Poitras ME, Almirall J. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. *BMC Fam Pract.* 2011;12:74.
46. Tinetti ME, Fried T. The end of the disease era. *Am J Med.* 2004;116(3):179-185.
47. Grol R. Development of guidelines for general practice care. *Br J Gen Pract.* 1993;43:146-151.
48. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess.* 2004;8(6):iii-iv, 1-72.
49. Van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. *The Lancet.* 2006;367:550-551.
50. Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. Current guidelines have limited applicability to patients with comorbid conditions: A systematic analysis of evidence-based guidelines. *PloS ONE.* 2011;6(10):e25987.
51. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. *Implement Sci.* 2009;4:54.\
52. Hughes LD, McMurdo ME, Guthrie B. Guidelins for people not for diseases: the challenges of applying IK clinical guidelines to people with multimorbidity. *Age Ageing.* 2013;42(1):62-69.
53. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. *BMJ.* 2012;345:e5205.
54. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev.* 2012;4:CD006560.
55. Ostini R, Hegney D, Jackson C, Williamson M, Mackson JM, Gurman K, et al. Systematic review of interventions to improve prescribing. *Ann Pharmacother.* 2009;43(3):502-513.

56. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev.* 2012;(6):CD000259.
57. Van Dijk L, Barnhoorn H, de Bakker D. Het Farmaco Therapie Overleg in 1999: stand van zaken en effecten op voorschrijven. Utrecht: *NIVEL*, 2001.
58. Florentinus SR, van Hulten R, Kloth ME, Heerdink ER, Griens AM, Leufkens HG, et al. The effect of pharmacotherapy audit meetings on early new drug prescribing by general practitioners. *Ann Pharmacother.* 2007;41(2):319-324.
59. Clyne B, Bradley MC, Hughes C, Fahey T, Lapane KL. Electronic prescribing and other forms of technology to reduce inappropriate medication use and polypharmacy in older people: a review of current evidence. *Clin Geriatr Med.* 2012;28(2):301-322.
60. NHG Doc. Wat is NHGDoc. Access date: 04-02-2017. [http://www.nhgdoc.nl/over-nhgdoc/].
61. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol.* 1992;45(10):1045-1051.
62. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
63. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008;46(2):72-83.
64. Vermeulen Windsant-van den Tweel AMA, Verduijn MM, Derijks HJ, van Marum RJ. Detectie van ongeschikt medicatiegebruik bij ouderen. Worden de STOPP- en START-criteria de nieuwe standaard? *Ned Tijdschr Geneeskd.* 2012;156:A5076.
65. NHG. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: *Nederlands Huisartsen Genootschap*, 2012.
66. Clyne W, Blenkinsopp A, Seal R. A Guide to Medication Review. Liverpool: *NHS National Prescribing Centre*, 2008.
67. Task Force on Medicines Partnership and The National Collaborative Medicine Management Services Programme. Room for review. A guide to medication review: the agenda for patients, practitioners and managers. London: *Medicines Partnership*, 2002.
68. Geurts MM, Talsma J, Brouwers JR, de Gier JJ. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. *Br J Clin Pharmacol.* 2012;74(1):16-33.
69. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol.* 2008;65(3):303-316.
70. Leendertse AJ, de Koning GH, Goudswaard AN, Belitser SV, Verhoef M, de Gier HJ, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. *J Clinl Pharm Ther.* 2013;38(5):379-387.
71. Willeboordse F, Schellevis FG, Chau SH, Hugtenburg JG, Elders PJM. The effectiveness of optimised clinical medication reviews in older people with geriatric problems in general practice: Opti-Med a cluster randomised controlled trial. *Submitted.* 2016.
72. Geurts MM, Stewart RE, Brouwers JR, de Graeff PA, de Gier JJ. Implications of a clinical medication review and a pharmaceutical care plan of polypharmacy patients with a cardiovascular disorder. *Int J Clin Pharm.* 2016;38(4):808-815.

73. Van Balen J, Damen-van Beek Z, Nelissen-Vrancken M, Verduijn M. Eindverslag Implementatie- en evaluatieproject Polyfarmacie bij ouderen. Utrecht: *NHG Nederlands Huisartsen Genootschap*, 2013.
74. Kringos DS, Boerma W, Hutchinson A, Saltman RB. Building primary care in a changing Europe. *WHO*, 2015.
75. Mossialos E, Wenzl M, Osborn R, Anderson C. International profiles of health care systems. 2014. *The Commonwealth Fund*, 2015.
76. NHG. Nederlands Huisartsen Genootschap. Richtlijn Adequate dossiervorming met het Elektronisch Patiëntendossier ADEPD. Utrecht: *NHG*, 2009.
77. Van Hassel DTP, Kasteleijn A, Kenens RJ. Cijfers uit de registratie van huisartsen. Utrecht: *NIVEL*, 2016.
78. Prins M, Hek K, Verberne L, Nielen M, Opperhuizen G, Verheij RA. Zorg door de huisarts. Jaarcijfers en trendcijfers 2010-2014. Utrecht: *NIVEL*, 2015.

Chapter 2

The prevalence of disease clusters in older adults with multiple chronic diseases – a systematic literature review

J. Sinnige
J.C. Braspenning
F.G. Schellevis
I. Stirbu-Wagner
G.P. Westert
J.C. Korevaar

PloS ONE. 2013; 8(11): e79641

ABSTRACT

Background: Since most clinical guidelines address single diseases, treatment of patients with multimorbidity, the co-occurrence of multiple (chronic) diseases within one person, can become complicated. Information on highly prevalent combinations of diseases can set the agenda for guideline development on multimorbidity. With this systematic review we aim to describe the prevalence of disease combinations (i.e. disease clusters) in older patients with multimorbidity, as assessed in available studies. In addition, we intend to acquire information that can be supportive in the process of multimorbidity guideline development.

Methods: We searched MEDLINE, Embase and the Cochrane Library for all types of studies published between January 2000 and September 2012. We included empirical studies focused on multimorbidity or comorbidity that reported prevalence rates of combinations of two or more diseases.

Results: Our search yielded 3070 potentially eligible articles, of which 19 articles, representing 23 observational studies, turned out to meet all our quality and inclusion criteria after full text review. These studies provided prevalence rates of 165 combinations of two diseases (i.e. disease pairs). Twenty disease pairs, concerning 12 different diseases, were described in at least 3 studies. Depression was found to be the disease that was most commonly clustered, and was paired with 8 different diseases, in the available studies. Hypertension and diabetes mellitus were found to be the second most clustered diseases, both with 6 different diseases. Prevalence rates for each disease combination varied considerably per study, but were highest for the pairs that included hypertension, coronary artery disease, and diabetes mellitus.

Conclusions: Twenty disease pairs were assessed most frequently in patients with multimorbidity. These disease combinations could serve as a first priority setting towards the development of multimorbidity guidelines, starting with the diseases with the highest observed prevalence rates and those with potential interacting treatment plans.

INTRODUCTION

The growing interest in the concept of multimorbidity, which refers to the co-occurrence of multiple (often chronic) diseases or medical conditions within one person[1], is motivated by the rising prevalence of multimorbidity, its negative health consequences, and the challenge to manage multimorbid patients in health care settings, often family medicine practice[2-11]. Managing patients with multimorbidity is much more complicated than managing patients with a single condition[10]. Clinical evidence-based guidelines have been developed to provide recommendations for patient management, to define standards of care, and focus efforts to improve quality. However, most clinical guidelines address single diseases, and do not always provide guidance for patients with multimorbidity. Simply combining the current disease oriented guidelines might result in a complex, inconvenient or even conflicting treatment regime, in terms of interactions between drugs and diseases, conflicting management strategies, and polypharmacy[10-12]. To support health care providers in daily practice, guidelines for combinations of diseases are thus warranted, especially for the most prevalent combinations with complex or incompatible regimes.

Despite the increasing body of research that has been conducted in the field of multimorbidity, there is still no clear, uniform operational definition for multimorbidity, and thus no clear picture of common multimorbidity combinations. Over the years, various methods have been developed and employed to measure multimorbidity. There are indices available that estimate a multimorbidity-score by weighting a range of diseases (e.g. Charlson Comorbidity Index[13] or Cumulative Illness Rating Scale[14]). Other applied multimorbidity measures are the Chronic Disease Score[15], RxRisk Model[16], or the Duke Severity of Illness Checklist[17]. Furthermore, multimorbidity can be assessed by simply counting the number of co-existing diseases within a person, using a predefined list of medical conditions. As disease counts are easy to use, it is presumably the most common approach to define multimorbidity.

Two recent systematic reviews described the available measures of multimorbidity in more detail and pointed out that the choice of a measure depends on the outcome of interest and the type of data available[18, 19]. Overall, these methods are employed to predict health outcomes, for instance, disability, quality of life, health care utilization or mortality. Additionally, these methods are often applied to assess prevalence rates. Prevalence estimates vary widely depending on the study population, setting, data sources, the type of the diseases considered and the number of conditions included in the analysis[18, 20-23].

Although evidence for the overall prevalence of multimorbidity is accumulating, insight into the prevalence of specific disease combinations (i.e. disease clusters) is limited. A

few studies explored disease clusters of multimorbidity by conducting statistical cluster or factor analysis[24-26]. These studies identified several broad clusters of diseases, but it remained unclear which specific combinations of diseases were most frequently occurring, taken into account the variation in prevalence rates. To the best of our knowledge, there are no systematic reviews that have investigated multimorbidity clusters, and therefore, a complete overview is still lacking.
With this current systematic review we aim to describe the prevalence of disease clusters in older patients with multimorbidity, as found in published studies. In addition, we intend to acquire information that can be supportive in the process of developing multimorbidity guidelines that could assist patient management and improve quality of health care.

METHODS

Search strategy

To find eligible studies we consulted the electronic databases MEDLINE/PubMed, Embase and Cochrane Library. A search strategy was developed for each database, using a combination of key words and Medical Subject Headings (MEDLINE) or Emtree terms (EMBASE and Cochrane Library). Since the term multimorbidity does not have an equivalent in the database's thesaurus, it was only searched as a key word. Until recently, the term comorbidity was used interchangeably with multimorbidity, as it also refers to the co-existence of multiple conditions[1, 27]. Hence, both terms and their spelling variations were included in our search algorithm. We combined search terms relating to multimorbidity (e.g. "multimorbid*", "multiple chronic diseas*", "multiple illness*"), comorbidity, chronic disease, and the definition or measurement (e.g. "index", "definition", "measurement", "list", "instrument"). The search strategy was developed iteratively to identify a combination of terms with an acceptable level of sensitivity and specificity. We restricted the search to articles with an available abstract, published in English or Dutch, and those published between January 2000 and September 2012. Before the year 2000, only a few articles had been published on the concept of multimorbidity. We did not restrict the search to a specific study type. To be complete, we also screened reference lists of all included articles. The final search strategy for MEDLINE is given in **Appendix 2.1**.

Study selection

The selection of studies followed several steps. First, different inclusion and exclusion criteria were specified for the selection of studies by title, abstract and full-text (**Table 1**). Second, a random sample of fifteen titles was screened by two authors (JS and JK) to control for unclear formulated inclusion and exclusion criteria, before screening all titles of the yielded articles; there was no disagreement or vagueness. Subsequently, one

author (JS) screened all titles for relevancy, based on the defined inclusion and exclusion criteria (**Table 1**). Third, two authors (JK and JS) independently appraised a sample of twenty abstracts. There was no disagreement between the two authors, after which all remaining abstracts were screened for eligibility by one author (JS) and, when necessary, by a second author (JK or JB). Last, full-text articles were independently screened for eligibility by at least two authors (JS screened all the full texts, and JK and JB both screened half of the full texts). To evaluate the full text articles on the inclusion and exclusion criteria, both authors appointed to screen the full text article filled out a self-constructed checklist. Discrepancies and ambiguities were solved by discussion between the two authors and, when necessary, by a third author.

Table 1. Inclusion and exclusion criteria of the screening process of the yielded articles.

Inclusion criteria		**Exclusion criteria**
Titles	- Included the words 'multimorbidity' or 'comorbidity' or related words (see step 1 and 2 in Appendix 2.1) *Titles not including these words were excluded*	- No data of disease combinations (or impossible to calculate prevalence rates)* - Age of at least half of the study population was ≤ 55 years - Diagnosis of a disease was based on medication prescription (ATC codes) only
Abstracts	- Evidence that multimorbidity/comorbidity was the outcome variable, or the central independent variable - Availability of a list of diseases to account for multimorbidity/comorbidity, morbidity indices or measures. *Abstracts not meeting these criteria were excluded.*	- Study size less than 500 persons† - Study conducted in a hospital setting‡ - Study examined solely two diseases§ - Study was focused on an index-disease with a prevalence < 0.5% in the total population in the Netherlands
Full-texts	- Availability of prevalence rates of specific disease clusters*	- Study with a non-empiric research type: 'letter', '(narrative) review', 'editorial', 'case-study', 'presentation', 'commentary'

** or results that allowed the calculation of a prevalence rate: Some studies reported odds ratios instead of prevalence rates. These data were converted into prevalence rates. If not possible, the article was excluded.*
† to include studies with results based on solid, robust data
‡ our study is more focused on primary care as health professionals in primary care often see patients with multiple health conditions
§ we assumed that studies solely focusing on two diseases would provide insufficient disease clusters with applicable prevalence rates

Assessment of study quality

After titles and abstracts had been screened, all remaining articles had an observational design. Therefore, quality assessment of the articles was based on several items of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist[28], which we included in our checklist. The items that were required to be described in the articles were (1) the study design; (2) the setting; (3) the study size; (4) eligibility criteria of participants; (5) the type of diseases included to measure comorbidity

or multimorbidity; (6) the data collection method; and (7) outcome data related to the prevalence of combinations of diseases. These items, with specific conditions, were also considered as inclusion and exclusion criteria (see also **Table 1**). In addition, to be retained in our review, only those articles that met our inclusion and exclusion criteria, and thus our specified quality standard, were selected.

Data extraction and synthesis

For each included study, the following data were extracted:

1. Study characteristics: First author, year of publication, country, study size, setting, population age;
2. Information relating to the number and types of diseases examined;
3. Information relating to (the prevalence of) the presented disease clusters.

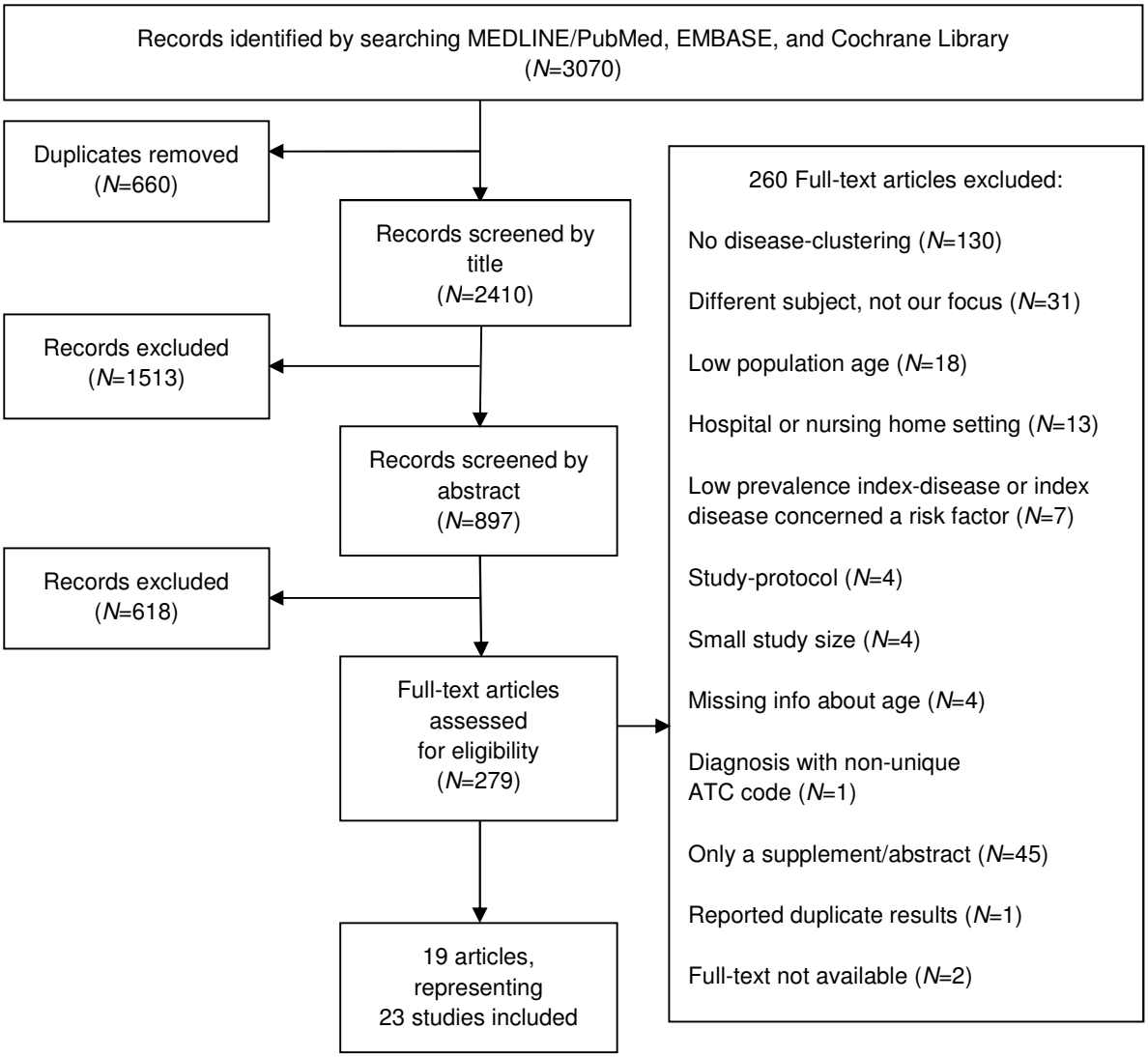
The checklist was employed to gather data about the study characteristics. These data were tabulated and ordered according to the population setting and the presence or absence of a specific index-disease. A mean age was given or calculated, but when impossible the age range was given. Subsequently, all possible diseases, and disease combinations as described in the included studies, were gathered, counted, and tabulated. In addition, the accompanying prevalence rates for each combination were collected and presented. When necessary, odds ratios were converted into prevalence rates. All given prevalence rates concerned the total study sample, and if not, prevalence rates were converted to relate to the total sample.

RESULTS

Included studies

In total, 3070 potentially eligible articles were identified, of which 2410 remained after exclusion of duplicates, see **Figure 1**. After screening of titles and abstracts, 279 articles remained to be read completely. Of these articles, 212 were excluded because they did not meet our inclusion criteria, as shown in **Figure 1**. Additionally, 45 articles were found to be an abstract or supplement for a congress and were excluded, 1 article was excluded because of double publication of part of the results of the same research project, and of 2 articles we had no access to the full-text. As a result, 19 articles remained. One of these articles focused on multimorbidity in different settings and described the data of these populations separately. These different settings were regarded as 5 individual studies and therefore, our final sample for analysis represented 23 studies. All 23 studies fulfilled our inclusion criteria and met our quality criteria.

Figure 1. PRISMA Flow chart outlining the study selection process.



Study characteristics

All 23 studies had an observational design and were conducted in either the general population (*n*=13)[23, 29-38], primary care (*n*=7)[23, 39-43] or ambulatory care setting (*n*=1)[44]. Two studies were based on data of the Veterans Health Administration system (VHA)[6, 45] (**Table 2**). The population size of the studies varied from 599[23] to over one million[45] individuals. Except for two[44, 45], all studies reported clusters of two diseases. In five studies[37, 38, 42, 43, 45] patients were only included when diagnosed with a specific disease (i.e. index-disease). In 8 studies[29, 30, 32-34, 36, 39, 40] prevalence rates were converted to provide comparable prevalence rates of the disease clusters. In one study, odds ratios were converted into prevalence rates[35].

Table 2. Characteristics of included studies examining clusters of comorbidity or multimorbidity.

	First author (year)	Country	Setting, (no. of partici-pants used in analyses), Mean age/ percentage	Data collection multi/co-morbidity	No. of diagnoses examined incl. index-disease	Index-disease	Type of diseases/ disease categories examined in the study									
							CVD	Diabetes	COPD/ asthma	Cancer	Musculo-skeletal	Depression/ anxiety	Dementia	Neurological	Eye/ ear	Digestive	Urinary
1	Fiest[29] (2011)	Canada	Gen. pop. (*n*= 15 591) 64 years	Interview with participants	12 (out of 19 diagnoses)	-	yes		yes		yes	yes		yes		yes	
2	Niti[30] (2007)	Singapore	Gen. pop. (*n*= 2 611) 66 years	Interview with participants	12	-	yes	yes	yes		yes	yes			yes	yes	
3	Marengoni[31] (2009)	Sweden	Gen. pop. (*n*= 1 099) 85 years	Physician's examination, hospital records, drug use and clinical examination	11 (out of 15 diagnoses)	-	yes	yes			yes	yes	yes		yes		
4	Kriegsman[32] (2004)	The Netherlands	Gen. pop. (*n*= 2 497) 69 years	Interview with participants	7	-	yes	yes	yes	yes	yes						
5	Fuchs[33] (2012)	Germany	Gen. pop. (*n*= 9 155) 56% 55-64 years 31% 65-74 years 13% ≥ 75 years	Interview with participants	6	-	yes		yes	yes	yes	yes				yes	
6	Lee P[34] (2009)	United States	Gen. pop. (*n*= 11 113) 55% 65-75 years 45% ≥ 76 years	Interview with participants	3 diseases and 2 syndromes	-	yes	yes									yes
7	Fillenbaum[35] (2000)	United States	Gen. pop. (*n*= 4 034) 73 years	Interview with participants	5	-	yes	yes		yes							

Table 2. (continued).

	First author (year)	Country	Setting, (no. of partici-pants used in analyses), Mean age/ percentage	Data collection multi/co-morbidity	No. of diagnoses examined incl. index-disease	Index-disease	Type of diseases/ disease categories examined in the study									
							CVD	Diabetes	COPD/ asthma	Cancer	Musculo-skeletal	Depression/ anxiety	Dementia	Neurological	Eye/ ear	Digestive	Urinary
8a	Schram[23] LASA* (2008)	The Netherlands	Gen. pop. (*n*= 2 463) 55-94 years	Interview with participants, validated by family physician	5 (out of 10 diagnoses)	-	yes		yes	yes	yes						
8b	Schram[23] The Rotterdam Study† (2008)	The Netherlands	Gen. pop. (*n*= 3 550) 65-99 years	Interview with participants validated by family physician, physical examination	4 (out of 15 diagnoses	-	yes	yes									
8c	Schram[23] Leiden 85-plus Study‡ (2008)	The Netherlands	Gen. pop. (*n*= 599) 85 years	Interview with family physician, electronic medical records	5 (out of 12 diagnoses)	-	yes			yes	yes	yes					
9	Mannino[36] (2008)	United States	Gen. pop. (*n*= 20 296) 60% ≥ 55 years	Interview with participants, clinical examination	4	-	yes	yes	yes								
10	Wesseling[37] (2013)§	The Netherlands	Gen. pop. (*n*= 979) 56 years	Survey with participants	19 (out of 25 diagnoses)	Osteoarthritis	yes	yes	yes		yes			yes		yes	yes
11	Lyketsos[38] (2005)	United States	Gen. pop. (*n*= 695) 82 years	Interview with participants	12 (out of 26 diagnoses)	Dementia or Other cognitive impairment	yes	yes			yes		yes	yes		yes	

Table 2. (continued).

	First author (year)	Country	Setting, (no. of partici-pants used in analyses), Mean age/ percentage	Data collection multi/co-morbidity	No. of diagnoses examined incl. index-disease	Index-disease	Type of diseases/ disease categories examined in the study										
							CVD	Diabetes	COPD/ asthma	Cancer	Musculo-skeletal	Depression/ anxiety	Dementia	Neurological	Eye/ ear	Digestive	Urinary
12	Pfaff[39] (2009)	Australia	Primary care (*n*= 20 183) 72 years	Survey with participants	15	-	yes	yes	yes	yes	yes	yes	yes	yes			
13	Schubert[40] (2006)	United States	Primary care (*n*= 3 013) 71 years	Electronic medical records	11	-	yes	yes	yes	yes	yes		yes			yes	yes
14	Van Oostrom[41] (2012)	The Netherlands	Primary care (*n*= 52 014) 43% 55-64 years 34% 65-74 years 23% ≥ 75 years	Electronic medical records	10 (out of 29 diagnoses)	-	yes	yes	yes	yes	yes	yes					
8d	Schram[23] CMR Nijmegen* (2008)	The Netherlands	Primary care (*n*= 2 895) 100% ≥ 55 years	Electronic medical records	6 (out of a total of 68 diagnoses)	-	yes†	yes			yes				yes		
8e	Schram[23] RNGP‡ (2008)	The Netherlands	Primary care (*n*= 5 610) 100% ≥ 55 years	Electronic medical records	6 (out of a total of 83 diagnoses)	-	yes	yes		yes	yes						
15	Noël[42] (2004)	United States	Primary care (*n*= 1 801) 77% ≥ 65 years	Interview with participants	11	Major depression or dysthymia	yes	yes	yes	yes	yes	yes		yes		yes	yes

Table 2. (continued).

	First author (year)	Country	Setting, (no. of partici-pants used in analyses), Mean age/ percentage	Data collection multi/co-morbidity	No. of diagnoses examined incl. index-disease	Index-disease	Type of diseases/ disease categories examined in the study										
							CVD	Diabetes	COPD/ asthma	Cancer	Musculo-skeletal	Depression/ anxiety	Dementia	Neurological	Eye/ ear	Digestive	Urinary
16	Struijs[43] (2006)	The Netherlands	Primary care (*n*= 7 499) 65 years	Electronic medical records	11	Diabetes mellitus	yes	yes	yes	yes	yes	yes		yes	yes		yes
17	Findley[45] (2011)	United States	VHA clinical services users (veterans) (*n*= 1 383 950) 90% ≥ 50 years	VHA electronic medical records and Medicare claims data	4	Diabetes mellitus, heart disease, hypertension	yes	yes				yes					
18	Lee T[6] (2007)	United States	VHA clinical services users (veterans) (*n*= 741 847) 100% 55-64 years	VHA electronic medical records	6 (out of 11 diagnoses)	-	yes	yes	yes	yes	yes						
19	Van den Bussche[44] (2011)	Germany	Ambulatory care (*n*= 123 224) 74 years	Claims data	19 (out of 46 diagnoses)	-	yes	yes	yes	yes	yes	yes			yes	yes	
							Total number of diseases/disease categories examined in all studies										
							23	**19**	**14**	**13**	**18**	**11**	**4**	**6**	**5**	**8**	**5**

Gen. pop.: General population; CVD: cardiovascular diseases; VHA: Veterans Health Administration system

** Schram et al. analyzed data from seven registries, these are presented separately. This is data from a population-based registry, LASA.*

† Schram et al. analyzed data from seven registries, these are presented separately. This is data from a population-based registry, The Rotterdam Study.

‡ Schram et al. analyzed data from seven registries, these are presented separately. This is data from a population-based registry, Leiden 85-plus Study.

§ During the search, this was still a provisional publication

|| Schram et al. analyzed data from seven registries, these are presented separately. This is data from a primary care registry, CMR Nijmegen.

¶ hypertension only

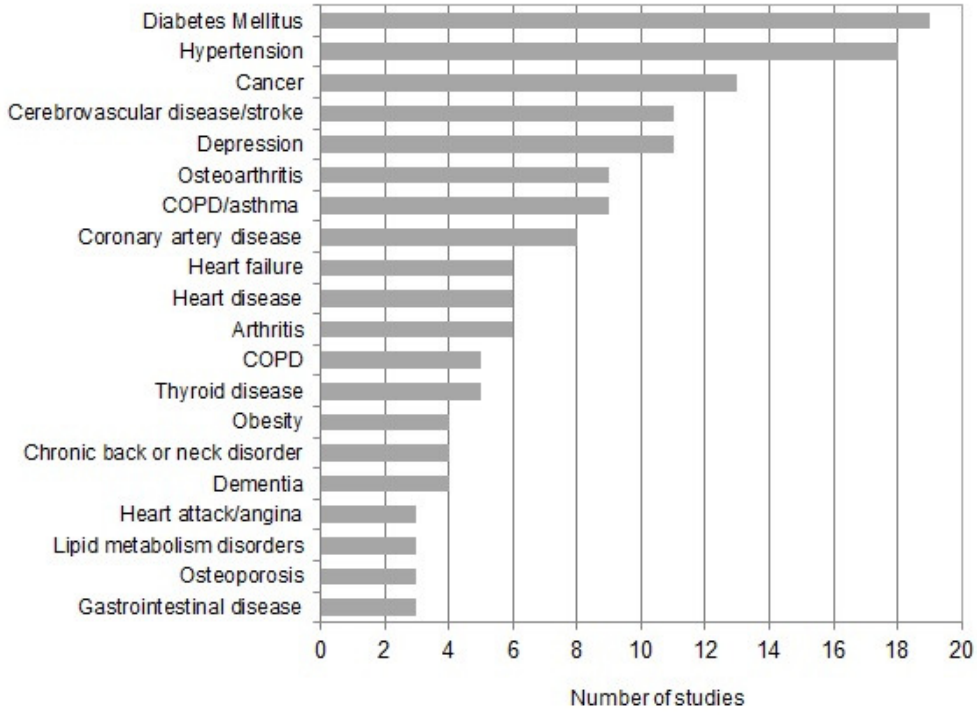
*** Schram et al. analyzed data from seven registries, these are presented separately. This is data from a primary care registry, RNGP.*

Type of diseases

Sixty-three different diseases were found, of which some were defined rather broadly (e.g. heart disease, gastrointestinal disease), while others were described in more detail (e.g. cataract, atrial fibrillation). Diabetes mellitus was the most frequently measured disease (described in 19 out of 23 studies). Other commonly assessed diseases were hypertension, cancer, stroke, and depression (**Figure 2**). Besides the 63 diseases, 165 combinations of two diseases (i.e. disease pairs) and 50 combinations of three diseases (i.e. disease triplets) were reported in the studies. Of the disease pairs, 20 were described rather frequently (≥ 3 studies), see **Table 3**. The disease triplets could not be replicated in any of the other studies and were therefore not further analyzed.

The rank in frequency of diseases examined in the included studies depended on the definition of the diseases. As displayed in **Figure 2**, various diseases of the circulatory tract were examined frequently (6 diseases in the top 20). However, the definition of these diseases differed in level of detail. If heart failure, coronary artery disease and heart attack/angina were defined as heart disease (this broad definition could comprise the separate diseases), heart disease was examined in 17 studies instead of in 6 (in some studies coronary artery disease and heart failure were both examined), making it the third most commonly assessed disease. This also applied the category COPD/asthma and the separate diseases asthma and COPD. If the specific diseases were grouped into the broad combined category, then COPD/asthma was investigated in 14 studies, instead of in 9 studies.

Figure 2. Type of diseases examined in the included studies (top 20).



Disease clusters

The most frequently assessed combinations concerned 12 different diseases (**Table 3**). Regarding these diseases, several clusters were identified. Of the assessed diseases, depression was most frequently clustered, and was paired with 8 other diseases. Additionally, hypertension and diabetes mellitus were also found to be commonly clustered in the available studies (with 6 different diseases). Although depression was the disease most frequently assessed in pairs, the highest prevalence rates were found for disease pairs including hypertension, highest for its combination with osteoarthritis (20%). The top ten disease combinations with the highest prevalence rates all included the diseases hypertension, coronary artery disease, and diabetes mellitus. In the studies that focused on a specific index-disease, mainly studies concerning depression, even higher prevalence rates were identified; 57% of the patients with a major depression were also diagnosed with hypertension (see **Table 4**).

Per study, varying prevalence rates for each disease combination were found. Especially for depression with hypertension (from 1.2% to 12.9%), and for cancer with hypertension (from 1.0% to 10.6%). Further, the highest prevalence values were often found in studies in which the morbidity data were collected via interviews or surveys. These studies almost always concerned the general population. Nearly all studies that applied electronic medical records (EMRs) to collect morbidity data were executed in a primary care setting.

DISCUSSION

While multimorbidity in older people seems to be the rule rather than the exception, evidence on the prevalence of specific disease clusters in patients with multimorbidity is limited. In this systematic review 19 articles were included, representing 23 studies, that described 63 diseases and 165 disease pairs. Twenty disease pairs, comprising 12 different diseases, were examined rather frequently. Of the assessed diseases, depression was the disease most frequently clustered, and was paired with 8 different diseases. Hypertension and diabetes mellitus were found to be the second most commonly clustered diseases, and were combined with 6 different diseases. The combinations with the highest prevalence rates included hypertension, coronary artery disease and diabetes mellitus.

Table 3. Prevalence of clusters of two diseases.

Disease	Clustered with	Prevalence per study (%; %; %), data gathered by an interview/survey*	Prevalence per study (%; %; %), data collected by patients' EMRs*	*No. of study**
Depression	Hypertension	**1.2**; 3.9; **7.6**; **12.9**		***1***, *12*, ***2***, ***8c***
	Arthritis	**1.7**; **2.8**; 4.9		***1***, ***2***, *12*
	Diabetes Mellitus	1.7; **2.8**	1.4	*12*, ***2***, *14*
	COPD/Asthma	**0.9**; 1.8		***2***, *12*
	Stroke	**0.2**; **0.9**; 1.0;	0.8; **1.1**	***1***, ***2***, *12, 14,* ***3***
	Cancer	1.1	0.9	*12, 14*
	Heart failure	0.7; **0.8**	0.7	*12,* ***2,*** *14*
	Heart disease		0.6	***1***
Hypertension	Osteoarthritis	**18.7**; **20.1**	3.2; 4.1; 9.1;	***8c***, ***8a,*** *18, 8e, 8d*
	Coronary artery disease	**9.8**; **14.9**	**7.6**	***7, 8a, 3***
	Diabetes Mellitus	**12.0**; **14.0**	**2.5**; 6.2; 6.4; 7.4	***8b, 7, 3,*** *8e, 18, 8d*
	Cancer	**5.5**; **10.6**	1.0; 3.4;	***7, 8c,*** *18, 8e*
	Depression	**1.2**; 3.9; **7.6**; **12.9**		***1,*** *12,* ***2***, ***8c***
	Dementia		2.9; **5.5**	*13,* ***3***
Diabetes Mellitus	Hypertension	**12.0**; **14.0**	**2.5**; 6.2; 6.4; 7.4	***8b, 7, 3,*** *8e, 18, 8d*
	Coronary artery disease	**4.1**; **4.5**	3.6	***7, 6,*** *14*
	Stroke	**0.6**; **2.9**	1.9	***4, 7,*** *14*
	Depression	1.7; **2.8**	1.4	*12,* ***2,*** *14*
	Heart failure	**1.8**	**1.8**; 2.2	***6, 3,****14*
	Cancer	**0.8**; **2.2**	1.9	***4, 7,*** *14*
Cancer	Hypertension	**5.5**; **10.6**	1.0; 3.4	***7, 8c,*** *18, 8e*
	Diabetes Mellitus	**0.8**; **2.2**	1.9	***4, 7,*** *14*
	Depression	1.1	0.9	*12, 14*
	Stroke	**0.5**; **0.9**	0.9	***4, 7****, 14*
Stroke	Diabetes Mellitus	**0.6**; **2.9**	1.9	***4, 7,*** *14*
	Dementia		0.4; **2.7**	*13,****3***
	Depression	**0.2**; **0.9**; 1.0	0.8; **1.1**	***1***, ***2,*** *12, 14,* ***3***
	Cancer	**0.5**; **0.9**	0.9	***4, 7****, 14*
Coronary artery disease	Hypertension	**9.8**; **14.9**	**7.6**	***7, 8a, 3***
	Heart failure	**2.8**	2.8; **5.6**	***6,*** *14,* ***3***
	Diabetes Mellitus	**4.1**; **4.5**	3.6	***7, 6,*** *14*
Heart failure	Coronary artery disease	**2.8**	2.8; **5.6**	***6,*** *14,* ***3***
	Diabetes Mellitus	**1.8**	**1.8**; 2.2	***6, 3,****14*
	Depression	0.7; **0.8**	0.7	*12,* ***2,*** *14*
Dementia	Hypertension		2.9; **5.5**	*13,* ***3***
	Stroke		0.4; **2.7**	*13,* ***3***
Osteoarthritis	Hypertension	**18.7**; **20.1**	3.2; 4.1; 9.1	***8c, 8a,*** *18, 8e, 8d*
Arthritis	Depression	**1.7**; **2.8**; 4.9		***1, 2,*** *12*
COPD/Asthma	Depression	**0.9**; 1.8		***2,*** *12*
Heart disease	Depression	**0.6**		***1***

Prevalence of disease clusters found in at least three studies

EMR: Electronic medical record

** Not bold: studies conducted in a primary care setting,* ***bold****: studies conducted in the general population,* *underlined: study based on VHA (Veterans Health Administration system) data.*

Table 4. Prevalence of clusters of two diseases, including an index-disease.

Index-disease	Clustered with	Prevalence per study, data gathered by an interview/survey*	Prevalence per study, data collected by patients' EMRs*	*No. of study**
Depression →	Hypertension	57.9		*15*
	Arthritis	55.6		*15*
	Diabetes Mellitus	23.2		*15*
	COPD/Asthma	23.3		*15*
	Cancer	10.9		*15*
	Heart disease	27.6		*15*
Hypertension →	Depression		16.7	*17*
Diabetes Mellitus →	Stroke		2.9	*16*
	Depression		3.9; 17.6	*16, 17*
	Cancer		2.7	*16*
Dementia →	Hypertension	**37.1**		***11***
	Stroke	**16.4**		***11***
Osteoarthritis →	Hypertension	**19.8**		***10***
Heart disease →	Depression		16.6	*17*

Prevalence of disease clusters found in at least three studies
EMR: Electronic medical record
** Not bold: studies conducted in a primary care setting, **bold**: studies conducted in the general population, underlined: study based on VHA (Veterans Health Administration system) data.*

The prevalence estimates of disease clusters differed widely among studies, a result that is in line with findings reported in other reviews[20, 46]. We will discuss two main possible explanations. First, differences in the population under study may affect the prevalence of multimorbidity and related disease clusters, like age, income, or ethnicity[47-52]. Multimorbidity is strongly associated with age[47-50]. Although we focused on older adults, the population's mean age still varied considerably (from 56 years to 85 years). Further, multimorbidity seems more common among people living in socioeconomically deprived areas or among people with a low income[47, 49, 50]. Second, variation in prevalence rates might be due to the applied definition of the diseases, the applied data collection method and the study setting[18-21, 53, 54]. In our review, some diseases were defined very broadly (e.g. cancer, heart disease) while other diseases were defined in more detail (e.g. osteoarthritis, atrial fibrillation). Studies executed in a primary care setting often applied medical records with information on a detailed level, yet they applied different classification codes with different definitions or based on different diagnostic methods (e.g. depression). In contrast, studies applied in the general population often used surveys or interviews, all inquiring about diseases differently. Other diseases, like obesity, are not always considered as a disease and therefore not included. As a consequence, few disease combinations and accompanying prevalence rates were identical.

With our current results we have identified combinations of diseases that are likely to co-occur and thus, a suitable treatment plan needs to be developed. Existing clinical practice guidelines, however, do not often address multimorbidity, and following all guidelines for all individual diseases may lead to a considerable treatment burden and to contradictory drug and self-care regimes[10, 11, 55]. Indeed, Boyd et al[10] reported that several potential medication interactions were found for a pattern that consisted of the diseases hypertension, diabetes mellitus, osteoarthritis, osteoporosis, and COPD. Contradicting life-style recommendations were found for osteoporosis and diabetes mellitus. As it is reasonable that our identified disease pairs are highly common in (elderly) adults, it would be useful if guidelines address potential drug interactions and contradicting treatment recommendations (drug-disease interactions, and disease-disease interactions) for these disease pairs.

This systematic review has some limitations. We used the term multimorbidity in our search process. This term is not well indexed in literature databases, and we might have missed some studies. To compensate for this constraint, we combined an extended list of text words referring to the term multimorbidity and we included the term comorbidity (with its possible spelling variations) to our search strategy. Next, we developed a scoring method based on several items of the STROBE checklist[28], and added these items to our strict inclusion and exclusion criteria, in order to obtain a minimal quality standard of all included studies. As a result, we could not differentiate further between levels of quality. Last, with this type of study we were restricted to merely describe the most *frequently explored* disease pairs in patients with multimorbidity, and not necessarily the *most occurring* disease pairs. Yet, the 12 identified diseases do represent highly prevalent diseases internationally[56, 57], and the accompanying combinations of these diseases are also likely to be highly prevalent.

Reflecting on our findings and limitations, more effort should be made to establish a multimorbidity disease list with uniformly defined diseases. Only by doing so, heterogeneity between study results can be diminished, and information about the prevalence and burden of multimorbidity will be more genuine and comparable. It seems also important to have a better understanding of specific treatment conflicts concerning certain disease clusters, and not merely by scrutinizing the existing guidelines, but by actually assessing daily practice according to guideline recommendations. In this regard, it seems practical to start with the most frequently occurring diseases. Furthermore, it is still valuable to gain more insight into (the prevalence of) specific co-occurring disease clusters, especially of clusters of three, and four diseases, as a large proportion of the elderly population is diagnosed with more than two chronic conditions[50]. For the development of a multimorbidity guideline, however, it might be easier to take into account rather small disease clusters instead of broad, comprehensive disease clusters[25, 26].

Conclusion

Management of care for (older) patients with multimorbidity can be challenging, or even burdensome. To be more concrete, health care professionals need to strike a balance between the various disease-specific guidelines before they can develop an appropriate treatment plan with feasible recommendations and advices, taking the patient's personal abilities into account. The disease clusters that we have distinguished, could serve as a first priority setting towards the development of multimorbidity guidelines. A likely option is to start with the most frequently occurring disease combinations, as regards the evaluation of potential treatment conflicts, the adjustment of existing clinical guidelines, or even the development of new guidelines.

References:

1. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature Comorbidity or multimorbidity: what's in a name? A review of literature. *Eur J Gen Pract*. 1996;2:65-70.
2. Uijen AA, Van de Lisdonk EH. Multimorbidity in primary care: Prevalence and trend over the last 20 years. *Eur J Gen Pract*. 2008;14 Suppl 1:28-32
3. Agborsangaya CB, Lau D, Lahtinen M, Cooke T, Johnson JA. Health-related quality of life and healthcare utilization in multimorbidity: results of a cross-sectional survey. *Qual Life Res*. 2013;22(4):791-799.
4. Kadam UT, Croft PR, Staffordshire North, GP Consortium Group. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. *Fam Pract*. 2007;24(5):412-419.
5. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL et al. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes*. 2004;2:51.
6. Lee TA, Shields AE, Vogeli C, Gibson TB, Woong-Sohn M et al. Mortality rate in veterans with multiple chronic conditions. *J Gen Intern Med*. 2007;22 Suppl 3:403-407.
7. Vyas A, Pan X, Sambamoorthi U. Chronic condition clusters and polypharmacy among adults. *Int J Family Med*. 2012;2012:193168.
8. Calderón-Larrañaga A, Poblador-Plou B, Gozález-Rubio F, Gimeno- Feliu LA, Abad-Díez JM et al. Multimorbidity, polypharmcay, referrals, and adverse drug events: are we doing things well? *Br J Gen Pract*. 2012; 62(605):e821-e826.
9. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162(20):2269-2276.
10. Boyd CM, Darer J, Boult C, Fried LP, Boult L et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716-724.
11. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing*. 2013;42(1):62-69.
12. Van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet*. 2006;367(9510):550-551.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
14. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16(5):622-626.
15. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol*. 1992;45(2):197-203.
16. Fishman PA, Goodman MJ, Hornbrook MC, Meenan RT, Bachman DJ et al. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. *Med Care*. 2003;41(1):84-99.
17. Parkerson GR Jr, Broadhead WE, Tse CK. The Duke Severity of Illness Checklist (DUSOI) for measurement of severity and comorbidity. *J Clin Epidemiol*. 1993;46(4):379-393.
18. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--A systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci*. 2011;66(3):301-311.

19. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: A systematic review and guide. *Ann Fam Med*. 2012;10(2):134-141.
20. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann Fam Med*. 2012;10(2):142-151.
21. Van den Akker M, Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. *J Clin Epidemiol*. 2001;54(7):675-679.
22. Taylor AW, Price K, Gill TK, Adams R, Pilkington R et al. Multimorbidity- not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health*. 2010;10:718.
23. Schram MT, Frijters D, Van de Lisdonk EH, Ploemacher J, de Craen AJM et al. Setting and registry characteristics affect the prevalence and nature of multimorbidity in the elderly. *J Clin Epidemiol*. 2008;61:1104-1112.
24. Cornell J, Pugh JA, Williams JW, Kazis L, Lee AFS et al. Multimorbidity clusters: Clustering binary data from multimorbidity clusters: clustering binary data from a large administrative medical database. *Appl Multivariate Res*. 2007;12(3):163-182.
25. Holden L, Scuffham PA, Hilton MF, Muspratt A, Ng SK et al. Patterns of multimorbidity in working Australians. *Popul Health Metr*. 2011;9(1):15.
26. Schäfer I, von Leitner EC, Schön G, Koller D, Hansen H et al. Multimorbidity patterns in the elderly: A new approach of disease clustering identifies complex interrelations between chronic conditions. *PLOS ONE*. 2010;5(12):e15941.
27. Fortin M, Lapointe L, Hudon C, Vanasse A. Multimorbidity is common to family practice: Is it commonly researched? *Can Fam Physician*. 2005; 51:244-245.
28. STROBE; STATEMENT. Strengthening the reporting of observational studies. Checklist for cohort, case-control, and cross-sectional studies. 2007. Accessed January 2013. [http://www.strobe.statement.org].
29. Fiest KM, Currie SR, Williams JVA, Wang J. Chronic conditions and major depression in community-dwelling older adults. *J Affect Disord*. 2011;131(1-3):172-178.
30. Niti M, Ng TP, Kua EH, Ho RC, Tan CH. Depression and chronic medical illnesses in Asian older adults: the role of subjective health and functional status. *Int J Geriatr Psychiatry*. 2007;22(11):1087-1094.
31. Marengoni A, Rizzuto D, Wang HX, Winblad B, Fratiglioni L. Patterns of chronic multimorbidity in the elderly population. *J Am Geriatr Soc*. 2009;57(2):225-230.
32. Kriegsman DMW, Deeg DJH, Stalman WAB. Comorbidity of somatic chronic diseases and decline in physical functioning: the Longitudinal Aging Study Amsterdam. *J Clin Epidemiol*. 2004;57(1):55-65.
33. Fuchs J, Busch M, Lange C, Scheidt-Nave C. Prevalence and patterns of morbidity among adults in Germany: Results of the German telephone health Interview survey German Health Update (GEDA) 2009. *Bundesgesundheitsbl*. 2012;55(4):576-586.
34. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: The health and retirement study. *J Am Geriatr Soc*. 2009;57(3):511-516.
35. Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. *J Gerontol A Biol Sci Med Sci*. 2000;55(2):M84-M89.

36. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J*. 2008;32(4):962-969.
37. Wesseling J, Welsing PMJ, Bierma-Zeinstra SMA, Dekker J, Gorter KJ et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip and Cohort Knee) study. *Rheumatology*. 2013;52(1):180-188.
38. Lyketsos CG, Toone L, Tschanz J, Rabins PV, Steinberg M et al. Population-based study of medical comorbidity in early dementia and "Cognitive Impairment, No Dementia (CIND)": association with functional and cognitive impairment: The Cache County Study. *Am J Geriatr Psychiatry*. 2005;13(8):656-664.
39. Pfaff JJ, Draper BM, Pirkis JE, Stocks NP, Snowdon JA et al. Medical morbidity and severity of depression in a large primary care sample of older Australians: the Deps-GP project. *Med J Aust*. 2009;190(7 Suppl):S75-S80.
40. Schubert CC, Boustani M, Callahan CM, Perkins AJ, Carney CP et al. Comorbidity profile of dementia patients in primary care: are they sicker? *J Am Geriatr Soc*. 2006;54(1):104-109.
41. Van Oostrom SH, Picavet HS, van Gelder BM, Lemmens LC, Hoeymans N et al. Multimorbidity and comorbidity in the Dutch population - data from general practices. *BMC Public Health*. 2012;12:715.
42. Noël PH, Williams JW Jr, Unützer J, Worchel J, Lee S et al. Depression and comorbid illness in elderly primary care patients: Impact on multiple domains of health status and well-being. *Ann Fam Med*. 2004;2(6):555-562.
43. Struijs JN, Baan CA, Schellevis FG, Westert GP, van den Bos GAM. Comorbidity in patients with diabetes mellitus: impact on medical health care utilization. *BMC Health Serv Res*. 2006;6:84.
44. Van den Bussche H, Koller D, Kolonko T, Hansen H, Wegscheider K et al. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. *BMC Public Health*. 2011;11:101.
45. Findley P, Shen C, Sambamoorthi U. Multimorbidity and persistent depression among veterans with diabetes, heart disease, and hypertension. *Health Soc Work*. 2011;36(2):109-119.
46. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A et al. Aging with multimorbidity: A systematic review of the literature. *Ageing Res Rev*. 2011:10(4):430-439.
47. Agborsangaya CB, Lau D, Lahtinen M, Cooke T, Johnson JA. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. *BMC Public Health*. 2012;12:201.
48. Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med*. 2005;3(3):223-228.
49. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-e21.
50. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43.
51. Mathur R, Hull SA, Badrick E, Robson J. Cardiovascular multimorbidity: the effect of ethnicity on prevalence and risk factor management. *Br J Gen Pract*. 2011;61(586):e262-e270.

52. Cabassa LJ, Humensky J, Druss B, Lewis-Fernández R, Gomes AP et al. Do race, ethnicity, and psychiatric diagnoses matter in the prevalence of multiple chronic medical conditions? *Med Care*. 2013;51(6):540-547.
53. Violán C, Foguet-Boreu Q, Hermosilla-Pérez E, Valderas JM, Bolíbar B et al. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. *BMC Public Health*. 2013;13:251.
54. Fortin M, Hudon C, Haggerty J, Van den Akker M, Almirall J. Prevalence estimates of multimorbidity: a comparative study of two sources. *BMC Health Serv Res*. 2010;10:111.
55. Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. Current guidelines have limited applicability to patients with comorbid conditions: A systematic analysis of evidence-based guidelines. *PLOS ONE*. 2011; 6(10):e25987.
56. Gommer AM, Poos MJJC. Welke ziekten hebben de hoogste prevalentie? In: *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid*. Bilthoven. 2010. Accessed January 2013. [http:// www.nationaalkompas.nl/].
57. World Health Organization. The global burden of disease 2004 update. Part 3: Disease incidence, prevalence and disability. 2008. Accessed January 2013. [http://www.who.int/healthinfor/global_burden_disease/2004_report_update/en/index.html]

Chapter 3

Multimorbidity patterns in a primary care population aged 55 years and over

J. Sinnige
J.C. Korevaar
G.P. Westert
P. Spreeuwenberg
F.G. Schellevis
J.C. Braspenning

Family Practice. 2015;32(5):505-513

ABSTRACT

Background: To support the management of multimorbid patients in primary care, evidence is needed on prevalent multimorbidity patterns.

Objective: To identify the common and distinctive multimorbidity patterns.

Methods: Clinical data of 120,480 patients (≥55 years) were extracted from 158 general practices in 2002–2011. Prevalence rates of multimorbidity were analyzed (overall, and for 24 chronic diseases), adjusted for practice, number of diseases and patients' registration period; differentiated between patients 55–69 and ≥70 years. To investigate multimorbidity patterns, prevalence ratios (prevalence rate index-disease group divided by that in the non-index-disease group) were calculated for patients with heart failure, diabetes mellitus, migraine or dementia.

Results: Multiple membership multilevel models showed that the overall adjusted multimorbidity rate was 86% in patients with ≥1 chronic condition, varying from 70% (migraine) to 98% (heart failure), 38% had ≥4 chronic diseases. In patients 55–69 years, 83% had multimorbidity. Numerous significant prevalence ratios were found for disease patterns in heart failure patients, ranging from 1.2 to 7.7, highest ratio for chronic obstructive pulmonary disease-cardiac dysrhythmia. For diabetes mellitus, dementia or migraine patients highest ratios were found for heart failure-visual disorder (2.1), heart failure- depression (3.9) and depression-back/neck disorder (2.1), respectively (all P-values <0.001).

Conclusions: Multimorbidity management in general practice can be reinforced by knowledge on the clinical implications of the presence of the comprehensive disease patterns among the elderly patients, and those between 55 and 69 years. Guideline developers should be aware of the complexity of multimorbidity. As a consequence of this complexity, it is even more important to focus on what matters to a patient with multimorbidity in general practice.

INTRODUCTION

Due to the aging of the population and improvements in medical care, a growing number of people are confronted with having one, and often multiple chronic conditions (i.e. multimorbidity)[1]. Prevalence estimates of multimorbidity ranged from 20–30% in persons of all ages, to 55–98% in persons 60 years and older, although these estimates are highly dependent on the measurement methods[2, 3]. Multimorbidity is related to negative health consequences, such as a poorer quality of life and functional status, higher rates of hospital admission and avoidable readmissions[4, 5].

Next to the negative effects on the patient, multimorbidity provides challenges to health care professionals, such as the GP, since traditional clinical practice guidelines focus on patients with a single disease. The question rises whether these guidelines support multimorbidity management[6-8]. Although studies have shown that the majority of the (reviewed) guidelines addressed the issue of comorbidity[7, 9], few guidelines gave management guidance in the presence of two or more conditions, and far less addressed the issue specific for older patients. As a result, experts in the field state that future guidelines should become more patient centered, integrate similar disease processes, and incorporate quality of life, risks, benefits and burden of recommended treatments for patients with multimorbidity[7, 10].

More insight into commonly occurring disease combinations (i.e. disease patterns) in the elderly could serve as a starting point for the development and formulation of evidence-based management plans for multimorbidity. Currently, consistent evidence about prevalence rates of multimorbidity patterns is lacking as available studies on the prevalence of disease combinations in (older) people[11] often have limitations. Most studies focus solely on disease pairs[12, 13] which might not reflect the true situation, as elderly patients often have more than two diseases. Another issue is the age group under study. Some studies underline that multimorbidity is also prevalent among patients of younger age[12], but little is known about the multimorbidity patterns. Finally, the classification of disease patterns is described by using statistical techniques (e.g. factor or cluster analysis[11]) that require specific assumptions of the data which cannot always be met.

The objective of this study is therefore, to identify highly prevalent, or prominent multimorbidity patterns in the elderly population. More specifically, two research questions are formulated:

1. What is the multimorbidity level for common chronic diseases in a primary care population aged 55 years and older, and the multimorbidity level in two distinct age groups?
2. Are there disease patterns that are significantly more or less prevalent in patients with a specific chronic disease compared to the population without that disease?

METHODS

Study population

We selected patients aged 55 years and older from general practices that participated in NIVEL Primary Care Database (formerly known as National Information Network of General practice (LINH)). This nationally representative database holds longitudinal data derived from patients' electronic medical records (EMRs) on for instance consultations, and morbidity, from about 90 Dutch general practices. The database includes a dynamic pool of practices and annually changes in composition[14]. In the Netherlands, all citizens are required to be registered with a general practice, and the GP has a gatekeeper role for access to specialized care. As records from the GP are likely to be most complete and reflect the total population, these are especially suitable for estimating prevalence rates of multimorbidity.

We selected practices that provided morbidity data for at least two complete consecutive years in the period 2002–2011. Quality checks on the data are part of the database protocol. Patients were required to be registered at the same practice for at least two full uninterrupted years. Diagnostic data were more accurate by using this minimum follow-up period, as for some chronic diseases patients do not necessarily visit their GP annually. Age of the patients was determined at start of their follow-up period. We only included patients diagnosed with at least one chronic condition, as we were interested in the prevalence and patterns of multimorbidity. This study was executed according to the precepts of the Dutch legislation on privacy and the regulations of the Dutch Data Protection Authority. According to Dutch legislation, studies using this type of observational data do not require medical ethical approval, or informed consent.

Selection of chronic diseases

In the Netherlands, diagnostic codes for diseases are recorded according to the International Classification of Primary Care (ICPC-1)[14], and GPs are expected to structure their EMR around disease episodes[16]. All patient contacts related to one health problem were clustered into a disease episode, constructed by using an algorithm to group ICPC-coded contact records from EMRs into episodes of care[17]. We used these disease episodes for the selection of chronic diseases. We chose 28 common chronic diseases[18], and added hypertension to the list due to its high prevalence rate in the elderly (although a risk factor rather than a disease). This resulted in 29 diseases listed with their ICPC codes in **Appendix 3.1**. A condition was included or present if there was a ICPC code corresponding to one of the selected diseases recorded in the patient's EMR during the complete follow-up period.

Statistical analysis

Multimorbidity level

The focus of this study was to determine the impact of diseases on the outcome per patient (i.e. multimorbidity yes/no). As a consequence, patients with multiple diseases were counted more than once, i.e. as often as their number of diseases. This would introduce bias; the disease specific multimorbidity proportions were biased towards the mean. To adjust for this phenomenon, we applied multilevel logistic regression analyses with a multiple membership structure[19]. With this technique, each patient is weighted by means of their diagnosed number of diseases. Further, patients (level 1) were nested within general practices, and practices and diseases were cross-classified at level 2. Based on the fact that not all patients had a full practice registration period, a correction factor was added to the models, accounting for the size of deviation from complete 10 years of registration. As a result, the intercept of the model was estimated as if all patients were considered to have a complete follow up of 10 years. The overall mean multimorbidity level (dependent variable) was estimated, and that for each of the chronic diseases included. The disease specific proportion was calculated as the sum of the overall adjusted rate, and the disease specific residual estimated from the disease level random effect[19]. Multilevel linear regression analyses were conducted with a similar model structure to analyze the overall adjusted mean number of diseases, and that for each chronic disease. All analyses were conducted for the total population, and separately for patients between 55 and 69 years, and ≥70 years. Diseases with a prevalence rate below 0.5% were excluded from these analyses. This since the number of patients diagnosed with one of the diseases was too minimal to ensure reliable prevalence rates assessed in the analyses. See **Appendix 3.2** for more information about the multiple membership analysis technique.

Multimorbidity patterns

Four chronic diseases were selected to examine their most prevalent disease patterns, and the degree of association between these patterns. The selection of these index-diseases was based on two criteria, namely (i) to cover the full range of multimorbidity levels (low versus high level of multimorbidity), and (ii) diseases that especially affected the elderly, since this patient group is most likely to be the target group with problems regarding treatment of multimorbidity. For each of the index-diseases, the most frequently co-occurring diseases were assessed, and those with a minimum prevalence rate of 10% were presented. Subsequently, prevalence ratios were calculated (i.e. prevalence rate of the disease pair within patients with the index-disease divided by the prevalence rate of the disease pair in patients without the index-disease). The ratios indicated whether the occurrence of a disease pair was higher or lower in patients with compared to patients without the index disease. The ratio's magnitude equals the strength of the relationship of that disease pair. Since the focus was on disease patterns within a specific patient group, crude data and descriptive statistics were used. Statistical significance of the ratios was assessed using chi-square tests. Descriptive statistics were performed to define the main

characteristics of the study population, by using STATA SE version 12.1, and the multilevel analyses were performed by using MLwiN version 2.30.

RESULTS

Initially, 170,583 persons aged 55 years and older were included. Prevalence numbers of five chronic diseases (i.e. HIV/aids, congenital cardiovascular anomaly, intellectual disability, schizophrenia and personality disorder) were less than 0.5%, and these diseases were therefore not included in the analyses. Further, 50,103 persons were not diagnosed with any of the 24 (i.e. 29 minus the five excluded diseases) diseases, and were therefore excluded. This resulted in a list of 24 chronic diseases among 120,480 patients, registered at 158 general practices. Patients' mean age was 67 years (SD 9.8), 45% were men, and 62% had multimorbidity (**Table 1**). Of the patients 55–69 years, and 70 years and older, 61% and 75% had multimorbidity, respectively.

Table 1. Demographic characteristics of the study population (patients aged ≥ 55 years diagnosed with at least one chronic disease in 2002-2011*).

	Total	Men	Women	P value†
Number of patients, (%)				
Total	120,480 (100.0)	54,375 (100.0)	66,105 (100.0)	
Multimorbidity (≥2 diseases)	74,733 (62.0)	32,420 (59.6)	42,313 (64.0)	<0.001
Mean age in years, (SD) ‡				
Total	66.9 (9.8)	65.7 (9.1)	67.9 (10.2)	<0.001
Multimorbidity	68.3 (9.8)	67.1 (9.3)	69.3 (10.2)	<0.001
Mean number of years follow up, (SD)				
Total	4.6 (2.3)	4.6 (2.3)	4.5 (2.3)	0.05
Multimorbidity	4.9 (2.4)	4.9 (2.4)	4.9 (2.4)	0.01

	Patients 55-69 years	Patients ≥70 year	P value†
Number of patients, (%)			
Total	75,310 (100.0)	45,170 (100.0)	
Multimorbidity (≥2 diseases)	41,866 (55.6)	32,867 (72.8)	<0.001
Mean age in years, (SD) ‡			
Total	60.4 (4.6)	77.6 (5.8)	<0.001
Multimorbidity	60.9 (4.7)	77.8 (5.7)	<0.001
Mean number of years follow up, (SD)			
Total	4.7 (2.4)	4.2 (2.2)	<0.001
Multimorbidity	5.2 (2.5)	4.5 (2.2)	<0.001

In this table, crude frequencies, percentages, and standard deviations (SD) are reported

** Minimum follow up period 2 years, maximum follow up 10 years*

† Statistical significance between men and women, and between patients 55-69 years and ≥70 years. Number of patients tested with Chi square tests, mean age, and mean follow up with T tests

‡ Patient's age at the year of inclusion

Multimorbidity level

The majority of the patients were diagnosed with more than one chronic disease (overall adjusted mean: 86%) (**Table 2**). The multimorbidity level ranged from 70% (migraine/hypertension) up to 98% (heart failure). In total, heart failure, heart valve disorder and a history of stroke were diseases that were significantly more often associated with multimorbidity (98%, 95% and 94%, respectively) compared to other diseases. On average, 83% of the patients aged 55–69 years and 94% of the patients 70 years and older were diagnosed with multiple chronic diseases. The highest multimorbidity level was found for heart failure, and the lowest for hypertension. Notably, in the oldest patients (i.e. 70 years and older) migraine had a relative high multimorbidity rate (97%), though it had nearly the lowest rate in patients 55–69 years (71%). Furthermore, dementia, Parkinson's disease and alcohol abuse turned out to be diseases with a relatively lower multimorbidity rate in patients aged 70 years and older. Results of the mean number of co-occurring diseases can be found in **Table 2**).

Disease patterns

Heart failure (high multimorbidity level), migraine (low multimorbidity level), diabetes mellitus (highly prevalent in the elderly) and dementia (specifically related to older age) were examined in more depth. Cluster diagrams (**Figures 1–4**) illustrate the associations between the most frequently co-occurring disease triplets.

Heart failure

Thirteen chronic diseases were highly common within heart failure patients, with prevalence rates varying from 10% (asthma) to 49% (hypertension) (**Figure 1**). Focusing on disease triplets, all prevalence ratios were statistically significant above 1.0, and 75% even above 2.0 (see **Appendix 3.3**). Prevalence ratios of the triplets including cardiac dysrhythmia were high; they were at least 6.0 for the combination with coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD) and osteoporosis. The same holds for the prevalence ratio of CAD-COPD (ratio 5.4), which was much higher in heart failure patients in comparison to patients without it. Focusing on some remarkable quartets (data not shown), almost 3% of the patients were diagnosed with both cardiac dysrhythmia, COPD and CAD. This prevalence rate was 14.2 times higher than that in the population without heart failure. The combination cardiac dysrhythmia-COPD-osteoporosis within heart failure had a ratio of 13.6.

Migraine

Prevalence ratios of many of the disease triplets were around 1.0 (**Figure 2**), indicating that the combinations for migraine were equally prevalent in patients with other chronic diseases (with the exception of chronic back or neck disorder with depression (ratio 2.1)). Seven combinations were less frequent in patients with migraine in comparison to those without migraine (ratio <0.8). In line with the frequently occurring triplet chronic back or

neck disorder-depression-migraine, the quartet that also included osteoarthritis had a ratio of 2.4 (prevalence rate 0.9%).

Diabetes mellitus
Regarding the disease triplets, heart failure was highly associated with visual disorder and with hypertension in patients with diabetes mellitus (ratios 2.1 and 2.0, respectively) (**Figure 3**). Other prevalence ratios of triplets that included diabetes mellitus and heart failure ranged between 1.5 and 2.0. More particularly common disease triplets were diabetes mellitus-CAD and COPD, or visual disorder, or hypertension, and diabetes mellitus-hypertension-visual disorder (see **Appendix 3.3**). Some distinct disease quartets were found (data not shown), especially the combination heart failure-visual disorder-hypertension (prevalence ratio 2.6). Further, the quartet chronic back or neck disorder-heart failure-visual disorder had a ratio of 2.4 within diabetes mellitus patients.

Dementia
Patients with dementia were more often diagnosed with heart failure and depression, heart failure and stroke and depression and stroke (ratios 3.9, 3.5 and 3.3, respectively) (**Figure 4**). There were four disease triplets with ratios between 2.5 and 3.0. Most quartets including stroke and depression plus one additional disease had prevalence ratios around 3.5. The quartet depression-stroke-diabetes-dementia, had a ratio of 6.2 (prevalence rate 0.9%).

When focusing on the patients aged 55–69 years, all ratios were higher for the patterns including heart failure, or diabetes mellitus, indicating that the identified disease combinations were even more specific for the index-disease patients (data not shown). For migraine, similar ratios were found since nearly all patients with migraine were younger than 70 years. For dementia, ratios were not calculated as almost all patients were older than 70 years.

DISCUSSION

This study showed that multimorbidity is the rule rather than the exception in primary care; not only for patients of 70 years and older, but also for patients of 55–69 years, as 83% (of those diagnosed with a chronic disease) presented multimorbid problems in the general practice. Multimorbidity is not restricted to disease pairs, but often consists of more extensive patterns (i.e. triplets, quartets) of chronic diseases. These patterns relate to complicated care needs that require change in general practice management.

Other studies confirm the high multimorbidity rate for many chronic diseases, for instance for heart failure or diabetes mellitus[11, 13], or confirm the finding that multimorbidity is

not just a problem of the elderly[12]. Yet, these studies did not focus on the complexity of multimorbidity (i.e. extensive disease patterns), especially not for patients younger than 70 years.

For four index-diseases, we identified the most common disease patterns of which some were specifically related to the index-disease and others were more common among the total population. Besides age as an explanation for the identified patterns, additional explanations for the co-occurrence of diseases are possible, as stated by van Weel and Schellevis[8]. They divided the co-occurrence of diseases into four categories namely, (i) diseases with a common pathophysiology, (ii) diseases that have developed due to complications of another disease, (iii) intercurrent multimorbidity which considers acute diseases in patients diagnosed with a chronic disease and (iv) concurrent diseases without any known causal relation between the diseases. Most of the diseases presented in our cluster diagrams have a common pathophysiology. For instance, cardiac dysrhythmia and CAD are both common causes of heart failure, and diabetes and hypertension are risk factors for heart failure[20]. Furthermore, the identified disease pattern diabetes mellitus-cardiac disease-COPD could be explained by shared cardiovascular and metabolic risk factors, such as hypertension and smoking. Visual disorder (e.g. retinopathy) as a common disease in diabetes mellitus patients can be considered as a complication of the presence of diabetes, and the same applies for dementia after stroke[21]. Some identified disease combinations have similar symptoms, leading to intensive diagnostic tests that could result in both diagnoses (e.g. COPD and heart failure)[20]. We found that COPD strongly clustered with CAD and cardiac dysrhythmia in heart failure patients. The intercurrence of multiple diseases could not be confirmed since our study did not focus on acute diseases. For some combinations, it is unclear how they are related, and if there is a causal relationship. These combinations could indicate concurrent co-occurring diseases, for instance cardiac dysrhythmia and osteoporosis in heart failure patients. Remarkably, disease patterns that included diabetes mellitus were less prevalent in migraine patients than in patients with other chronic diseases. A few studies do confirm the 'protective' effect of diabetes on migraine[22]. Considering the variation within the disease patterns, it may be useful to explore the patterns of disease for other common index-diseases.
The cluster diagrams showed that hypertension was highly prevalent in all four chosen index-diseases. This is also confirmed in other studies exploring disease pairs and triplets[11, 13]. The current study, moreover, showed that the ratios for hypertension and other diseases were not quite prominent, underlining that hypertension is not specifically related to one certain type of disease. Only in the cluster diagram for diabetes mellitus some distinct combinations were found that included hypertension. In a study by Islam et al[11], it was found that diabetes and hypertension were always classified in the same cluster or group, using several analytic techniques. In a study by Marengoni et al[13], cluster analysis revealed a cluster consisting of heart failure-hypertension-atrial fibrillation-CAD. These diseases are also highly prevalent, and strongly clustered (i.e. high prevalence

ratios), in our cluster diagram of heart failure. A second cluster found by Marengoni et al was dementia, depression and hip fracture[13]. Our study showed that depression was highly prevalent in dementia patients, and it clustered strongly with most cardiac diseases, and with osteoarthritis.

With the applied study design, we were able to provide reliable prevalence rates of common disease patterns in an elderly population. Data of a large sample of patients were available and minimal selection bias exists as the practices included are representative for the Netherlands. Furthermore, information related to chronic diseases is most likely complete in general practice registries since the GP acts as gatekeeper for secondary care. Recording in EMRs is most likely accurate as practices also used their files for reimbursements. Possible bias due to patients' perception of the presence of a chronic illness, or other factors that are related to the accuracy of self-reported disease diagnosis[3], is excluded when using EMR data. Another major strength of this study is the use of the multiple membership technique. Most studies do not account for the fact that older patients often are diagnosed with multiple diseases and thus are counted several times in multimorbidity prevalence estimations. With the multiple membership technique, this bias is eliminated by weighting each patient by means of their number of diseases.
This study also has some limitations. Although quality requirements regarding data recordings exist, possible mistakes in ICPC recording could have been made, for instance due to typing errors or incorrect coding. Though, it is not likely that errors occurred systematic differently for the index-disease and non-index-disease group. Further, it may be possible that GPs differ in their decision of reporting a chronic disease diagnosis, for instance for diagnoses that rely on more subjective criteria (e.g. depression). However, we have taken this into account by the correction for practice in the statistical model. In addition, one can argue whether the disease depression reflects a chronic depression. Although no information about the diagnostic method was available, the ICPC-1 codes for depression were classified in the 'diagnosis section' of the ICPC-1 classification system. This considers a more definitive diagnosis than a registration in the 'symptoms/and complaints section'. Another limitation relates to the data sample. We consider the large data sample of patients as a strength of this study, but to account for the variance in follow-up period of the patients we adjusted for the years of registration. As a result, the overall adjusted mean is somewhat overestimated since it considers the mean multimorbidity level as if all patients were registered for the complete follow-up period of 10 years. Further, although the data were collected within a 10-year period, we could not determine the direction of the identified associations. This since we determined whether a disease was present (yes/no) after the follow-up period, but did not determine which disease was diagnosed first, or second, or last. Another issue for consideration is that we have determined patients' age at moment of inclusion. This means that some patients, that were classified to the 55–69 years group, turned 70 years during their follow-up period. If other age categories were chosen, some of the patients moved from the 'younger' category to the

'older' category, which could have altered the results. Yet, the overall findings, including the cluster diagrams, would have been unchanged and still demonstrate that multimorbidity is most often characterized by the presence of complex disease patterns.

As older people frequently visit their GP, findings from this study seem particularly relevant to GPs. The multimorbidity patterns displayed in this study illustrate the heterogeneous nature of this patient group[10]. Patients with multimorbidity differ widely as regards the possible diagnosed diseases. Since they are also heterogeneous in terms of their disease severity, functional status, or prognosis this may lead to a great variety in different treatments considered by the GP. GPs should be aware of the fact that not only patients of 70 years and older, but also those between 55 and 70 years have complex health care needs and require complex management. Further, they should keep in mind that the proportion of patients, for which recommendations reported in current practice guidelines are limited applicable, might be even larger than one expects, and that this is already true for younger elderly. As a consequence, the workload for the GP might be higher than expected due to more time consuming consultations. Due to the large extent of all possible disease combinations, it seems unrealistic to develop new guidelines for all possible combinations. Therefore, GPs may need other information, skills and tools to provide optimal care for this patient group. For instance, to inquire about patient preferences during a consultation, and to integrate these preferences into medical decision making. This requires patient's ability to prioritize their preferences for care, and to weigh risks and benefits of the treatment and the various decision options given by the GP. In turn, it requires skills and time from the GP to discuss all options with the patient.

Conclusions

This study stresses the complexity of multimorbidity, and the challenges to provide (high quality) care for patients with multimorbidity by GPs. Guideline developers should be aware of this complexity, and GPs should focus on what matters to the patient, rather than on what is the matter in this patient group.

Table 2. Multimorbidity level and number of co-occurring diseases in patients diagnosed with at least one out of 24 chronic diseases, 2002-2011.

	Total			Patients aged 55-69 years			Patients aged ≥70 years†		
	% multimorbidity (95% CI)*	Mean no. of diseases (95% CI)*,‡	N	% multimorbidity (95% CI) *	Mean no. of diseases (95% CI) *,‡	N	% multimorbidity (95% CI)*	Mean no. of diseases (95% CI) *,‡
Overall mean	**85.6 (82.9–88.0)**	**3.25 (3.11–3.40)**	**75310**	**83.4 (80.2–86.1)**	**3.04 (2.89-3.18)**	**45170**	**93.5 (92.2–94.6)**	**3.96 (3.83-4.10)**
Heart failure	98.4 (96.0–99.4) +	4.97 (4.31–5.63) +	2323	98.5 (96.2–99.4) +	5.06 (4.39-5.73) +	7197	97.4 (94.6–98.8) +	4.71 (4.14-5.28) +
Heart valve disease	94.5 (87.1–97.8) +	3.99 (3.34–4.65) +	1031	93.7 (85.3–97.4) +	3.60 (2.94-4.27)	1266	95.4 (90.9–97.7)	4.43 (3.87-4.98)
Stroke	94.0 (86.0–97.6) +	3.74 (3.08–4.40)	3008	92.7 (83.0–97.1)	3.48 (2.81-4.15)	4076	94.8 (89.5–97.5)	3.96 (3.39-4.53)
Cardiac dysrhythmia	91.0 (79.8–96.3)	3.66 (3.00–4.32)	4983	85.8 (69.8–94.0)	3.17 (2.50-3.85)	5797	96.7 (93.2–98.4)	4.41 (3.85-4.98)
Coronary artery disease	88.8 (75.5–95.3)	3.39 (2.73–4.05)	10108	85.9 (69.9–94.1)	3.09 (2.41-3.76)	9037	94.1 (88.1–97.2)	4.01 (3.44-4.58)
Diabetes Mellitus	88.5 (75.0–95.2)	3.23 (2.57–3.89)	15781	87.4 (72.7–94.8)	3.06 (2.38-3.73)	11226	93.1 (86.1–96.7)	3.77 (3.20-4.34)
COPD	88.1 (74.1–95.0)	3.40 (2.74–4.06)	8073	86.1 (70.4–94.2)	3.17 (2.49-3.84)	6623	93.1 (86.2–96.7)	3.97 (3.40-4.54)
Visual disorder	88.0 (74.1–95.0)	3.38 (2.72–4.04)	5964	82.6 (64.5–92.5)	2.98 (2.31-3.66)	7420	92.7 (85.5–96.5)	3.79 (3.22-4.35)
Dementia	85.4 (69.5–93.8)	3.26 (2.60–3.92)	422	85.0 (69.3–93.5)	3.13 (2.47-3.79)	3127	84.1 (71.0–91.9) -	3.25 (2.68-3.82) +
Rheumatoid arthritis	85.4 (69.5–93.7)	3.28 (2.62–3.94)	2138	81.6 (62.9–92.0)	2.95 (2.28-3.62)	1540	95.1 (90.1–97.6)	4.26 (3.70-4.82)
Parkinson's disease	84.5 (68.1–93.3)	3.23 (2.57–3.88)	450	81.6 (63.5–91.8)	2.94 (2.28-3.60)	963	86.6 (75.3–93.2) -	3.45 (2.89-4.01)
Asthma	84.4 (67.8–93.3)	3.24 (2.57–3.90)	6303	83.4 (65.7–92.9)	3.05 (2.38-3.72)	2471	96.7 (93.3–98.4)	4.70 (4.13-5.26) +
Anxiety disorder	83.9 (67.0–93.0)	3.21 (2.55–3.87)	2462	81.9 (63.5–92.2)	3.03 (2.36-3.70)	1084	96.2 (92.4–98.1)	4.40 (3.85-4.96)
Osteoporosis	83.3 (66.0–92.8)	3.22 (2.56–3.88)	4017	77.5 (56.9–90.0)	2.86 (2.18-3.53)	3964	92.6 (85.4–96.4)	3.91 (3.35-4.48)
Hearing disorder	83.3 (66.0–92.8)	3.15 (2.49–3.81)	3750	76.3 (55.2–89.3)	2.74 (2.07-3.41)	4326	92.3 (84.7–96.2)	3.78 (3.21-4.35)
Osteoarthritis	82.3 (64.3–92.3)	3.03 (2.37–3.69)	11275	77.3 (56.5–89.9)	2.75 (2.08-3.43)	9212	92.3 (84.8–96.3)	3.72 (3.15-4.29)
Depression	82.0 (63.9–92.2)	3.10 (2.44–3.76)	6289	79.3 (59.4–90.9)	2.88 (2.20-3.55)	3469	94.4 (88.8–97.3)	4.18 (3.62-4.75)
Chr. back or neck disorder	79.0 (59.3–90.6)	2.95 (2.29–3.61)	12166	76.4 (55.3–89.5)	2.75 (2.08-3.43)	5439	94.7 (89.3–97.5)	4.17 (3.60-4.74)
Alcohol abuse	78.5 (58.8–90.3)	2.89 (2.23–3.55)	1294	81.2 (62.5–91.8)	2.93 (2.26-3.60)	234	87.8 (78.5–93.4) -	3.65 (3.13-4.17)
Cancer	77.3 (57.0–89.8)	2.85 (2.19–3.51)	10222	72.7 (50.5–87.5)	2.62 (1.95-3.30)	8257	88.8 (78.5–94.5)	3.48 (2.91-4.05)
Epilepsy	76.8 (56.6–89.4)	2.98 (2.33–3.64)	874	73.5 (51.8–87.8)	2.77 (2.10-3.44)	490	93.2 (87.1–96.5)	4.03 (3.50-4.57)
Burnout	75.9 (55.1–89.0)	2.74 (2.08–3.40)	1938	77.5 (57.0–90.0)	2.73 (2.06-3.40)	350	93.6 (88.1–96.6)	4.05 (3.53-4.58)
Hypertension	69.9 (47.4–85.7)	2.57 (1.91–3.23) -	35726	68.1 (44.9–84.8)	2.46 (1.79-3.14)	22932	81.0 (66.3–90.2) -	3.04 (2.46-3.61) -
Migraine	69.9 (47.5–85.6)	2.62 (1.96–3.28)	2316	71.2 (48.6–86.6)	2.62 (1.95-3.30)	348	96.7 (93.9–98.2) -	4.02 (3.50-4.55)

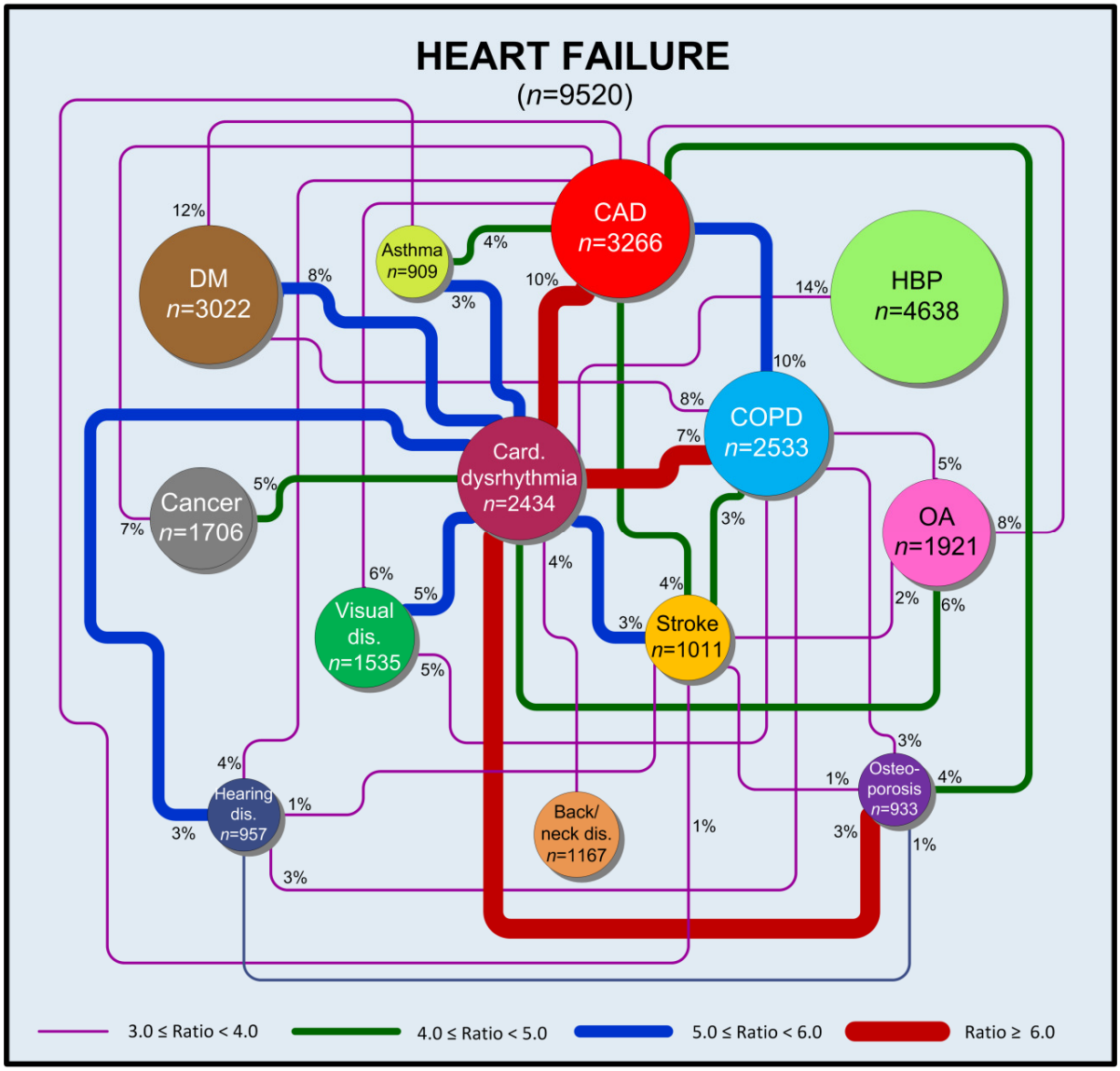
N=number of patients; CI=confidence interval; Sign=significance; chr=chronic. Percentages (95% CI), and mean number of diseases are adjusted for the practice level, disease level (number of diseases), and the registration period at the practice (i.e. years of follow up with a minimum period of 2 years and a maximum period of 10 years).

** Disease outcome (i.e. multimorbidity level, mean no. of diseases) was statistically significant higher(+) or lower(-) ($p<0.05$) than the overall mean outcome.*

† Between patients 55-69 years and patients ≥ 70 years, there was a statistically significant difference ($p<0.05$) in the proportion of patients with multimorbidity (except for heart valve disorder and visual disorder).

‡ Mean no. co-occurring diseases including the concerning disease

Figure 1. Cluster diagram of the most common disease patterns in patients with heart failure.



CAD = coronary artery disease; Card. = cardiac; dis. = disorder; DM = diabetes mellitus; HBP = high blood pressure; HF = heart failure; OA = osteoarthritis. Cluster diagrams of the most common chronic diseases (with a prevalence rate of ≥10%) and disease patterns in patients with the index diseases heart failure (i), migraine (ii), diabetes mellitus (iii) or dementia (iv). Size of the circles is proportional to the number of patients diagnosed with that disease; the n in the circle refers to the number of patients with both the index-disease and a co-occurring disease (e.g. in this figure, 3022 patients were diagnosed with both heart failure and diabetes mellitus). Lines display statistically significant prevalence ratios of the observed prevalence rate of that combination within patients with the index-disease divided by the prevalence rate of that combination in the population without the index-disease (i.e. the non-index-disease population). Width of the lines reflects the magnitude of the ratio. Percentages refer to the percentage of that combination within the index-disease population (e.g. in this figure, of the heart failure patients 5% were also diagnosed with COPD and osteoarthritis). In this figure, crude prevalence rates were presented. To increase the visibility of this diagram, ratios with a minimum of 3.00 were presented (see ***Appendix 3.3*** *for all ratios).*

Figure 2. Cluster diagram of the most common disease patterns in patients with migraine (see Figure 1 legend for more details).

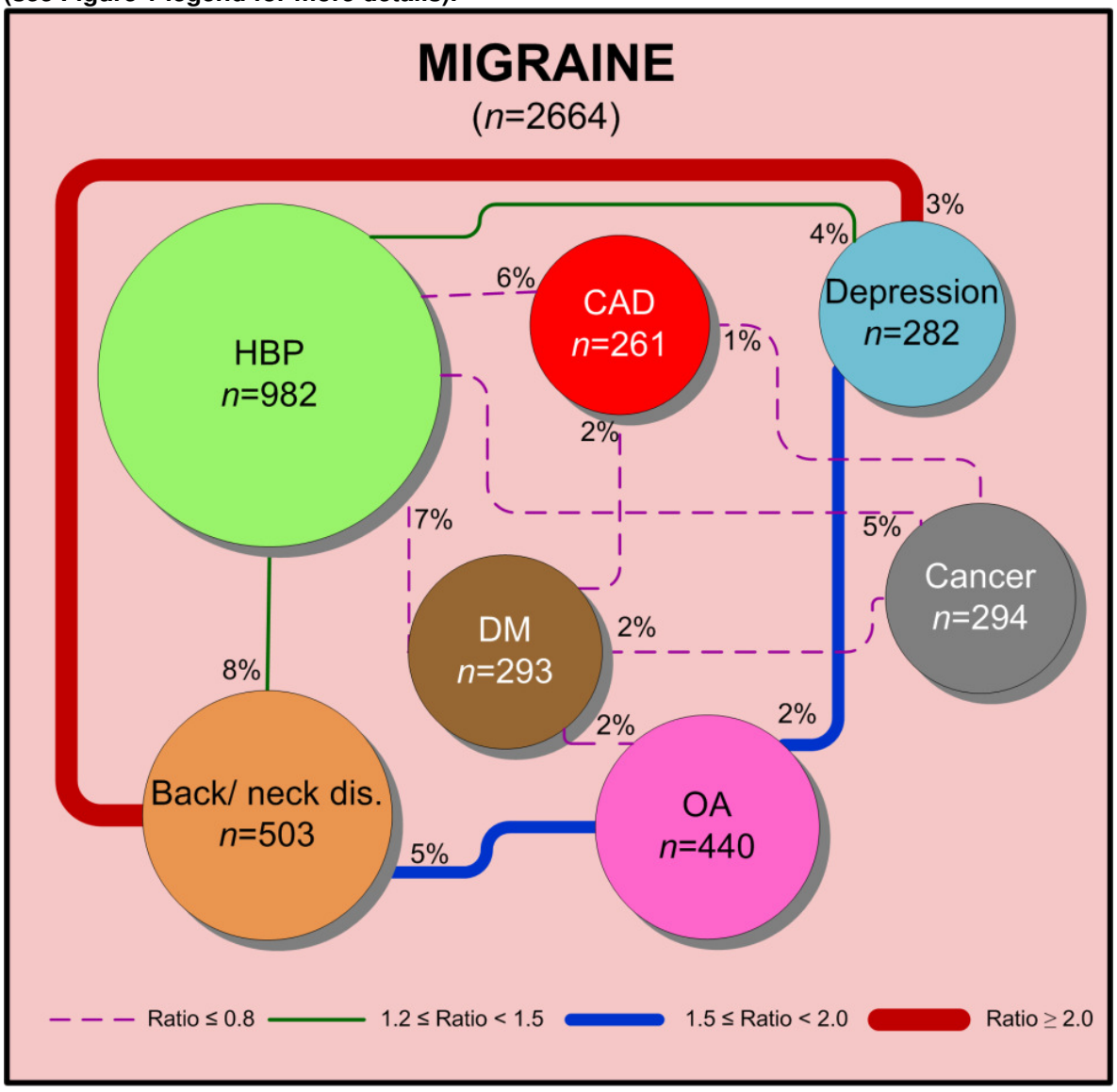


Figure 3. Cluster diagram of the most common disease patterns in patients with diabetes mellitus (see Figure 1 legend for more details).

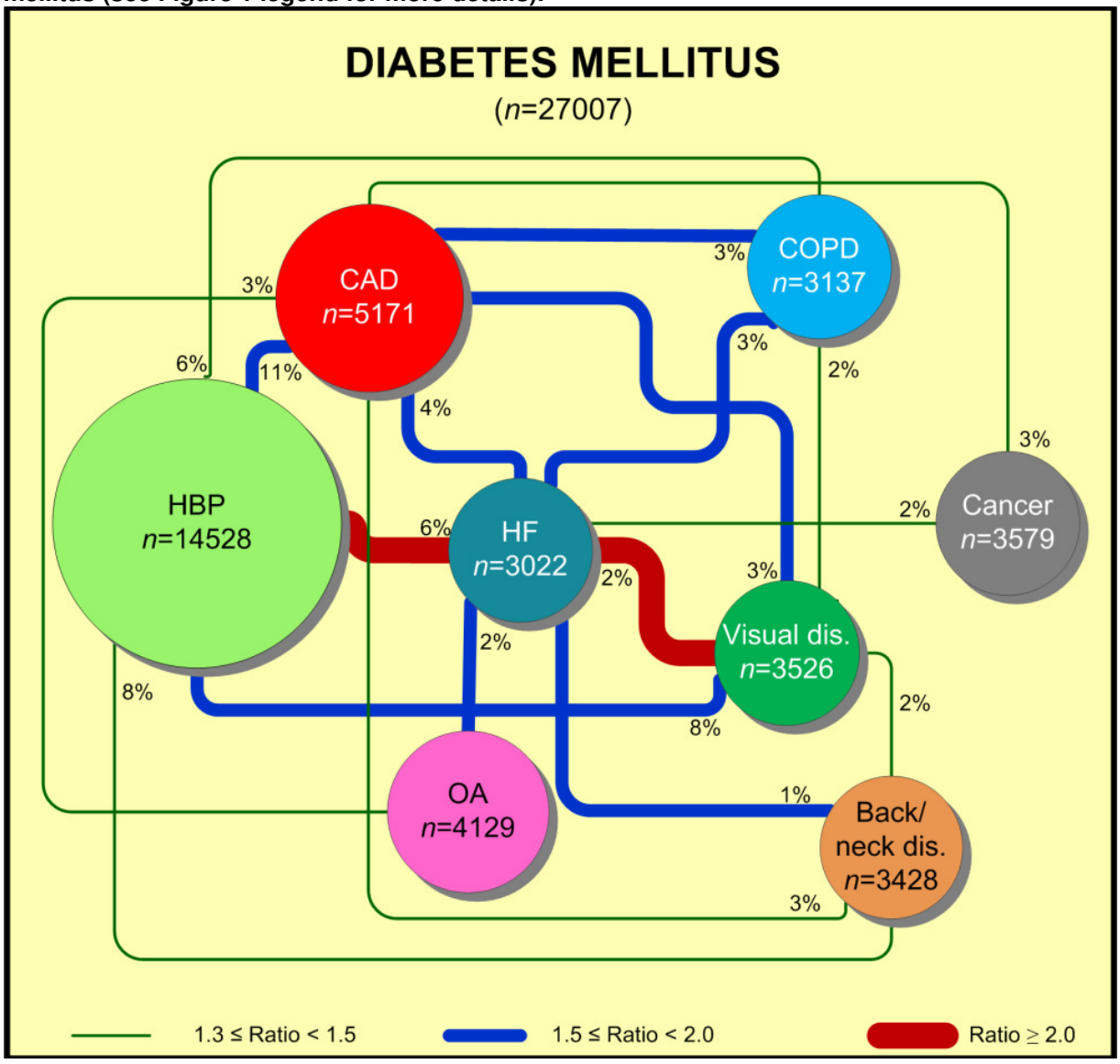
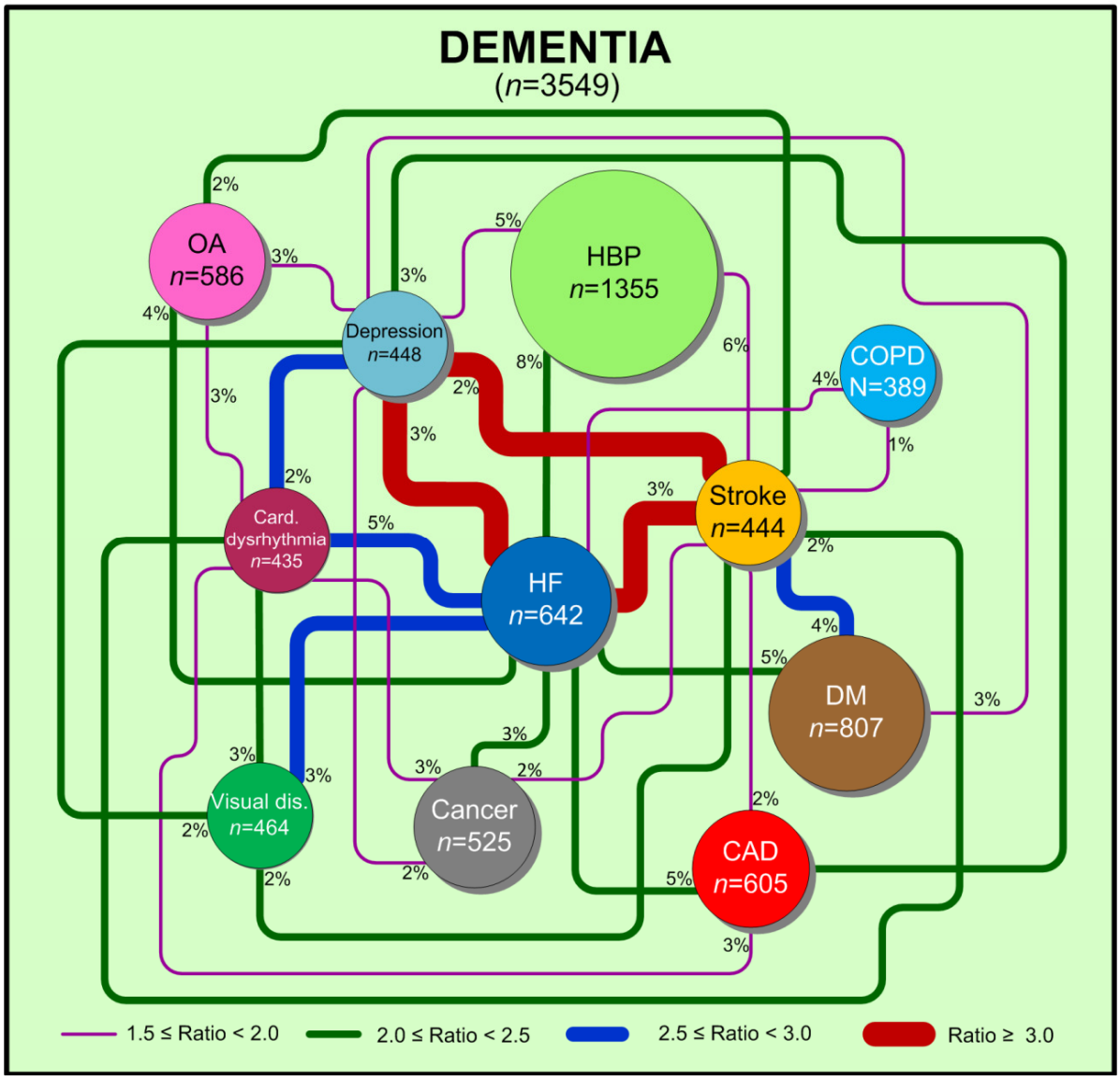


Figure 4. Cluster diagram of the most common disease patterns in patients with dementia (see Figure 1 legend for more details).



References:

1. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. *Eur J Gen Pract*. 1996;2:65-70.
2. Fortin M, Steward, M, Poitras ME Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med*. 2012;10(2):142-151.
3. Sinnige J, Braspenning J, Schellevis F, Stirbu-Wagner I, Westert G, Korevaar J. The prevalence of disease clusters in older adults with multiple chronic diseases - A systematic literature review. *PloS ONE*. 2013;8(11):e79641.
4. Kadam UT, Croft PR, North Staffordshire GP Consortium group. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. *Fam Pract*. 2007;24(5):412-419.
5. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162(20):2269-2276.
6. Tinetti ME, Bogardus ST, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med*. 2004;351(27):2870-2874.
7. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716-724.
8. Van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet*. 2006;367(9510): 550-551.
9. Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. *PLoS ONE*. 2011;6(10):e25987.
10. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. Guiding principles for the care of older adults with multimorbidity: An approach for clinicians. *J Am Geriatr Soc*. 2012;60(10):E1-E25.
11. Islam MM, Valderas JM, Yen L, Dawda P, Jowsey T, McRae IS. Multimorbidity and comorbidity of chronic diseases among the senior Australians: prevalence and patterns. *PloS ONE*. 2014;9(1):e83783.
12. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43.
13. Marengoni A, Rizzuto D, Wang HX, Winblad B, Fratiglioni L. Patterns of chronic multimorbidity in the elderly population. *J Am Geriatr Soc*. 2009;57(2):225-230.
14. Verheij RA. Over NIVEL Zorgregistraties: geschiedenis en achtergrond. Uit: *NIVEL Zorgregistraties eerste lijn*. 2013. Accessed July 2014. [www.nivel.nl/node/3464].
15. Lamberts H, Wood M. The birth of the International Classification of Primary Care (ICPC). Serendipity at the border of Lac Leman. *Fam Pract*. 2002;19(5):433-435.
16. NHG Nederlands Huisartsen Genootschap. NHG-Richtlijn Adequate dossiervorming met het Elektronisch Patiëntendossier ADEPD. Derde versie. Utrecht. 2013.
17. Biermans MC, Elbers GH, Verheij RA, Jan van der Veen W, Zielhuis GA, Robbé PF. External validation of EPICON: a grouping system for estimating morbidity rates using electronic medical records. *J Am Med Inform Assoc*. 2008;15(6): 770-775

18. Hoeymans N, van Oostrom SH, Gijsen R, Schellevis FG. Selectie van chronische ziekten. Volksgezondheid Toekomst Verkenning. *Nationaal Kompas Volksgezondheid.* RIVM: Bilthoven. Accessed July 2014. [http://www.nationaalkompas.nl].
19. Goldstein H, Rasbash J, Browne W, Woodhouse G, Poulain M. Multilevel models in the study of dynamic household structures. *Eur J Popul*. 2000;16(4):373-387.
20. Lindenfeld J, Albert NM, Bohmer JP, Collins SP, Ezekowitz JA, Givertz MM et al. Executive Summary: HFSA 2010 Comprehensive heart failure practice guideline. *J Card Fail*. 2010;16(6):475-539.
21. Leys D, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. *Lancet Neurol*. 2005;4(11):752-759.
22. Berge LI, Riise T, Fasmer OB, Hundal O, Oedegaard KJ, Midthjell K et al. Does diabetes have a protective effect on migraine? *Epidemiology*. 2013;24(1):129-134.

Chapter 4

Inter-practice variation in polypharmacy prevalence amongst older patients in primary care

J. Sinnige
J.C. Braspenning
F.G. Schellevis
K. Hek
I. Stirbu
G.P. Westert
J.C. Korevaar

Pharmacoepidemiology and Drug Safety. 2016;25(9):1033-1041

ABSTRACT

Purpose: Complex medication management in older people with multiple chronic conditions can introduce practice variation in polypharmacy prevalence. This study aimed to determine the inter-practice variation in polypharmacy prevalence and examine how this variation was influenced by patient and practice characteristics.

Methods: This cohort study included 45,731 patients aged 55 years and older with at least one prescribed medication from 126 general practices that participated in NIVEL Primary Care Database in the Netherlands. Medication dispensing data of the year 2012 were used to determine polypharmacy. Polypharmacy was defined as the chronic and simultaneous use of at least five different medications. Multilevel logistic regression models were constructed to quantify the polypharmacy prevalence variation between practices. Patient characteristics (age, gender, socioeconomic status, number, and type of chronic conditions) and practice characteristics (practice location and practice population) were added to the models.

Results: After accounting for differences in patient and practice characteristics, polypharmacy rates varied with a factor of 2.4 between practices (from 12.4% to 30.1%) and an overall mean of 19.8%. Age and type of conditions were highly positively associated with polypharmacy, and to a lesser extent a lower socioeconomic status.

Conclusions: Considerable variation in polypharmacy rates existed between general practices, even after accounting for patient and practice characteristics, which suggests that there is not much agreement concerning medication management in this complex patient group. Initiatives that could reduce inappropriate heterogeneity in medication management can add value to the care delivered to these patients.

INTRODUCTION

In older people, who are frequently diagnosed with multiple (chronic) conditions[1], regular use of multiple different medications is common[2]. As a consequence, appropriate prescribing is often not that simple or apparent for physicians[3-5]. On the one hand, prescribing according to recommendations stated in practice guidelines may result in an excessive amount of medications which, in turn, may lead to poor adherence and adverse effects[6-8]. On the other hand, when deciding not to prescribe an additional medication, uncertainty remains about potential benefits of the omitted medication to the patient[9, 10]. Overall, for patients with multiple chronic conditions, who are usually treated in primary care, several pharmaceutical treatment options seem possible and adequate, influenced by the physician's and the patient's perspective, which may lead to variation in medical behavior and practice variation[11, 12]. More focused on the number of medications prescribed for a patient, complex medication management might result into practice variation as regards the number of patients with multiple medications or polypharmacy.

Polypharmacy is the simultaneous use of several medications and is often defined as the chronic use of at least five different medications[2, 13, 14]. Polypharmacy has been associated with reduced medication adherence, an increased risk for potentially inappropriate medication use, adverse drug reactions, and unplanned hospitalizations[6-8]. Studies have demonstrated that a higher age, lower socioeconomic status (SES), a higher number, and the type of diagnosed conditions are suggested to be positively associated with polypharmacy. Findings of a gender effect are inconsistent[2, 6, 15].

When variation in medication prescribing, and polypharmacy, cannot be justified or explained by differences in the patient population and their clinical characteristics[16-18], this points towards other factors involved in decision-making on a higher level (practice level), for instance, contextual factors, or a lack of consensus about the chosen pharmaceutical treatment[11, 12]. Available studies on practice variation and medication prescribing focused on the use of potentially inappropriate medications in older patients[8, 19, 20], and to our knowledge, only one study examined the broader concept of polypharmacy in relation to practice variation[21]. They found a six fold variation between practices in the prevalence rate of polypharmacy; part of this variation could be explained by practice structure, workload, and prescribing profile. Although they adjusted for age and gender, other assuming relevant patient characteristics were not included in this study[21].

Quantifying and understanding practice variation as regards polypharmacy prevalence is relevant, as it can highlight the complexity in managing these patients and may provide

clues to facilitate prescribing medications in this patient group. Therefore, the aim of this study was to examine the inter-practice variation of the prevalence of polypharmacy amongst older patients in primary care and how this is influenced by patient and practice characteristics. Based on previous studies[2, 6, 15, 17, 22, 23] our hypothesis was that patient characteristics (age, gender, SES, and chronic conditions) were associated with polypharmacy and could explain part of the variation between practices, and we hypothesized that some of the practice variation could be explained by differences in practice population. In some general practices, physicians might be more experienced with managing older complex patients with polypharmacy, which could result in less uncertainty in management. In previous studies[8, 17, 20], it was found that the type of practice or practice size and the practice location were associated with (high risk) prescribing. Our hypothesis was that practice size could explain some practice variation because in larger practices, several physicians share work environment and cultural aspects and can therefore have a more similar prescribing behavior than physicians from different practices[12].

METHODS

Database and study population

In this cohort study, we used linked data from routine electronic medical records (EMR) of general practices that participate in a network of a representative sample of practices in the Netherlands, the NIVEL Primary Care Database (NIVEL-PCD)[24], and from dispensing data of a sample of public pharmacies that supplied data to a pharmacy-dispensing registration database (i.e. the Foundation for Pharmaceutical Statistics, SFK)[25]. The general practitioner (GP) in the Netherlands, and several other countries, has a gatekeeper role for access to specialized care[26]. As a result, EMR records from the GP are likely to be most complete, hold information from other health care professionals like medical specialists, who manage the patient as well, and include the total population as all Dutch inhabitants are obligatory listed to a GP. The sample of participating pharmacies in NIVEL-PCD is representative as regards age and gender, compared with the total sample of pharmacies in the Netherlands[27]. Linkage was based on matching records from variables available in both data sources, namely, gender, year of birth, four-digit postal code, date of dispensing/prescribing, and the Anatomic Therapeutic Classification code (ATC) of a medication (i.e. A10BA02 metformin). Linkage was accepted if at least half of the prescriptions (NIVEL-PCD) matched with the dispensed medications (SFK) within a lag period of 0–6 days[28]. We included older patients, specified as those aged 55 years and older, who were registered on the full calendar year of 2012 in a participating general practice. From NIVEL-PCD, we extracted demographic information and morbidity data from patients' EMRs. To determine polypharmacy, information about the chronic usage of patients' prescribed medications was needed. Accurate information about the duration of

a prescription and its daily dosage was available in the SFK database. Dispensed data from SFK was also considered more complete as regards the medications prescribed in specialized care, rather than prescription data from NIVEL-PCD. Moreover, dispensed data represent actual usage of medications more closely than prescription data as the medications were actually distributed from the pharmacy to the patient. Therefore, from SFK, we extracted data of patients' dispensed medications. Of the population aged 55 years and older with at least one prescription (117,232 patients) 45,731 patients from 126 general practices participating in NIVEL-PCD were identified in 120 pharmacies that supplied data to SFK (mean number of prescriptions linked population vs. non-linked population 22.3 and 22.8, respectively).

Measures

Polypharmacy

The definition of polypharmacy (no/ yes) was derived from the Dutch multidisciplinary guideline of Polypharmacy in the elderly[29]; five or more chronically used medications with different ATC codes at the third level (e.g., R03B), which were used simultaneously for at least 1 day in 2012. Chronic usage was defined as four or more prescriptions of a medication (i.e. similar ATC codes at the third level) or a medication prescribed for at least 90 days[29]. See **Box 1** for more information.

Box 1. Additional information related to the operationalization of the outcome variable polypharmacy.

For the prescription duration period, recorded information about the amount of doses dispensed by the pharmacist and about the daily defined dose for the patient was applied. The prescribed periods of all chronically used medications determined whether five or more different medications were used simultaneously for at least 1 day in 2012 (i.e. polypharmacy). Dermatologicals for topical usage were excluded of the count because these medications usually do not interact with other (systemic) medications[29]. Antibiotics (i.e. ATC codes "J01") were also not taken into account because they are almost exclusively prescribed for acute infections. For some dispensed prescriptions, there was no or incorrect information about the dispensed dosage or daily prescribed dosage. For these prescriptions (11% of all prescriptions in the dataset), the prescribed period was considered the period between the first and last dispensing date of that medication. We have set 120 days between two dates as the maximum number of days to be considered as a consecutive period. If there were more than 120 days between two dates, this was considered as a gap in using.

Patient characteristics

We included age, gender, SES, the number of chronic diseases, and the type of chronic diseases in the analyses. Age was divided in seven 5-year categories (55 to ≥85 years). For

SES, a 'status score' was applied, based on patients' four-digit postal codes (neighborhood level), developed by the Netherlands Institute for Social Research[30]. It was established in 2010 with four indicators (mean income, the proportion of people with a low education level, low income, and unemployed). Similar to previous studies[30, 31], we divided the scores into quintiles, and patients with a score in the highest and lowest quintile indicated patients living in a neighborhood with a high and low SES, respectively. Scores of patients within the middle three quintiles indicated patients living in a neighborhood with a medium SES. Based on previous studies, we selected 29 chronic diseases using constructed disease episodes of recorded morbidity data from GPs' EMRs[32, 33]. The number of chronic diseases was divided into three categories (0–1 chronic disease, 2–4 diseases, and ≥5 diseases). Multimorbidity was defined as two or more chronic diseases (no/yes).

Practice characteristics

Three measures on GPs' experience with managing complex patients were studied. The measures were "proportion elderly patients" operationalized as the proportion patients of ≥70 years in a practice from the total practice population, "proportion patients from a low SES neighborhood" and "proportion multimorbid patients". The variable "proportion patients from a low SES neighborhood" was divided in three categories (i.e. 0–10%, 10–50%, and ≥50%) because of the skewness of the data. We also analyzed the practice type (i.e. solo, duo, and group), the practice's degree of urbanization in three categories (highly, moderate, and not urbanized) and practice size (i.e. small, medium, and large), based on the practices' number of listed patients divided into tertiles.

Statistical analysis

Descriptive statistics described the study population. To examine inter-practice variation in polypharmacy prevalence, we constructed multilevel logistic multivariate regression models with patients (level 1) clustered within general practices (level 2), polypharmacy as the dependent variable, the patient and practice variables as determinants, and the practice level as random effect. In order to test our hypotheses, the first model included the patient-related variables gender, age, SES, and number of chronic conditions as determinants. In model 2, we added 29 types of chronic conditions, and it considered the full model as regards the patient-related variables. In model 3, the practice population variable "proportion patients with multimorbidity" was added, as well as the variable concerning the practices' degree of urbanization. The other variables on practice level were not included into the multivariate model because their p-values were ≥0.20 when adding them to model 2 separately. All determinants were centered on their mean to make the results more interpretable. In all models, we adjusted for the practice's type of electronic medical record software system to account for possible differences in registration methods. Only patients with complete data were included in the multilevel analysis, and practices with a minimum number of 50 patients to estimate robust models. Besides the odds ratio (OR), 95% confidence interval (CI), and p-value indicating the

association between polypharmacy and the determinants, we reported the practice variance component as an estimation of the variance of the polypharmacy rate between practices (i.e. a decrease in value between the models indicated a decrease in the inter-practice variation). Further, we reported the proportion change in variance, indicating the proportion of variance explained by adding explanatory variables. The 95% coverage interval of the practice variance components indicated the range in the practices' difference in the proportion polypharmacy patients that cannot be explained by the covariates. This coverage interval was calculated in the following way: Intercept ± 1.97 sqrt (between practice variance), which was transformed back to the probability scale. The average polypharmacy prevalence per general practice was also estimated by using an empirical Bayes estimator[34]. All analyses were performed using STATA SE version 13.0 and MLwiN version 2.30. A p-value below 0.05 was considered statistically significant.

RESULTS

Population characteristics

Of the patients, 27% had polypharmacy, and they were on average 5 years older than those without polypharmacy (72 vs. 67 years), lived more often in a neighborhood with a low SES (20% compared with 16%), and showed more multimorbidity (90% vs. 46%; **Table 1**). The number of medications used in the polypharmacy group was on average 11.2 of which 6.9 was used chronically. Information about the practice characteristics is shown in **Table 2**.

Inter-practice variation

For the multilevel analyses, data of 44,917 patients from 86 practices (mean no. of patients per practice (SD); 525 (464)) were studied because for 235 patients data on SES was missing and 40 practices (with 579 patients) had less than the required number of patients. In model 1 (**Table 3**), the overall mean polypharmacy rate was 21.4%. The practice variance component was 0.07 (SE= 0.01), which corresponds to a 95% coverage interval of 14.1–31.0, meaning that the polypharmacy prevalence ranged from 14% to 31% between practices. The number of chronic conditions was most strongly positively associated with polypharmacy (OR 36.4, 95%CI 32.8-40.3, for ≥5 chronic conditions). After including the type of chronic conditions into the model (model 2), only having 2–4 conditions compared with 0 or 1 condition was still significantly associated with polypharmacy. Nearly all chronic conditions were positively associated with polypharmacy, most strongly cardiac conditions (heart failure: OR 5.25, 95%CI 4.59-6.00; coronary artery disease: OR 6.50, 95%CI 6.02-7.02). The practices' difference (95% coverage interval) in adjusted polypharmacy prevalence ranged from 12.1% to 31.6%. For model 2, the average proportion of patients with polypharmacy in each practice separately is presented in **Figure 1**.

Table 1. Descriptive characteristics of the study population: patients aged ≥ 55 years with at least one prescribed medication in 2012, divided by patients with and without polypharmacy.

	No polypharmacy (*N*= 33,449)		Polypharmacy (*N*= 12,282)		*P*-value*
	N	%	*N*	%	
Male	15,279	45.7	5,702	46.4	0.155
Female	18,170	54.3	6,580	53.6	
Age, mean (SD)	66.6 (8.7)		72.4 (9.5)		<0.001
Age groups:					<0.001
55-59 years	8,220	24.6	1,214	9.9	
60-64 years	7,859	23.5	1,664	13.5	
65-69 years	6,583	19.7	2,134	17.4	
70-74 years	4,467	13.3	2,088	17.0	
75-79 years	3,105	9.3	2,108	17.2	
80-84 years	1,900	5.7	1,677	13.6	
≥ 85 years	1,315	3.9	1,397	11.4	
SES categories†					<0.001
High	5,044	15.2	1,477	12.1	
Medium	22,772	68.4	8,275	67.8	
Low	5,472	16.4	2,456	20.1	
Mean no. of chronic conditions (SD) ‡	1.6 (1.3)		3.4 (1.6)		<0.001
Number of chronic conditions:					
0	6,916	20.7	133	1.1	<0.001
1	11,054	33.0	1,118	9.1	
2	8,516	25.5	2,738	22.3	
3	4,341	13.0	3,166	25.8	
4	1,770	5.3	2,468	20.1	
5	636	1.9	1,459	11.9	
≥ 6	216	0.6	1,200	9.7	
Multimorbidity §	15,479	46.3	11,031	89.8	<0.001
Mean no. of medications (SD) ¶	4.5 (2.9)		11.2 (4.2)		<0.001
Mean no. chronically used medications (SD) ||	1.7 (1.4)		6.9 (2.1)		<0.001
Number of chronically used medications:					
0	8,424	25.2	0	0.0	<0.001
1-4	24,715	73.9	0	0.0	
5-9	310	0.9	10,838	88.2	
10-14	0	0.0	1,377	11.2	
≥ 15	0	0.0	67	0.6	

Note: Total N=45,731 patients, 126 practices. SD= standard deviation.

** Statistical significance tested with Chi-squared tests (binary variables) or T-tests (continuous variables).*

† Socioeconomic status (SES) on neighborhood level (i.e. four-digit postal code).

‡ Based on a list of 29 chronic conditions[32].

§ ≥ 2 chronic conditions out of the list of 29 chronic conditions[32].

¶ Medication on the third Anatomic Therapeutic Classification level.

|| Medication on the third Anatomic Therapeutic Classification level, with at least four prescriptions, or those used for minimal 90 days (excluding the dermatologicals and antibiotics).

After accounting for the patient population, in some practices, there were still at least twice as many patients with polypharmacy than in other practices (a factor 2.6 difference). In model 3, including the practice variables, the practices' range (95% coverage interval) in polypharmacy prevalence varied from 12.4% to 30.1% indicating that there was a factor 2.4 difference as regards the polypharmacy prevalence between practices after including all explanatory variables, with an overall mean of 19.8%. Practices located in moderately and

low urbanized areas had a significantly lower odds ratio of polypharmacy than practices located in very strong or strong urbanized areas.

Table 2. Characteristics of the general practices, and the number of patients per practice variable.

	Practices (*N*=126)		Patients (*N*=45,731)	
	N	**%**	***N***	**%**
Type of practice				
Single-handed practices	69	54.8	20,174	44.1
Duo practices	40	31.7	14,803	32.4
Group practices	17	13.5	10,754	23.5
Practice size *				
Small	76	60.3	15,336	33.5
Medium	33	26.2	16,698	36.5
Large	17	13.5	13,697	30.0
Degree of urbanization (location of the practice):				
(Very) strong	67	53.2	19,185	41.9
Moderate	28	22.2	10,176	22.3
Little or not	31	24.6	16,370	35.8
Practice population characteristics				
Mean % patients ≥70 years (SD)	11.4	(3.92)	-	
Mean % patients living in a low SES neighborhood (SD) †	26.4	(28.8)	-	
Mean % patients with multimorbidity (SD)	20.1	(4.18)	-	
Mean no. of pharmacies per practice (SD) ‡	2.28	(1.20)	-	
Electronic medical record software type:				
A	63	50.0	22,047	48.2
B	9	7.1	2,783	6.1
C	12	9.5	3,630	7.9
D	34	27.0	12,207	26.7
E	7	5.6	5,063	11.1
F §	1	0.8	1	<0.01

SD= standard deviation

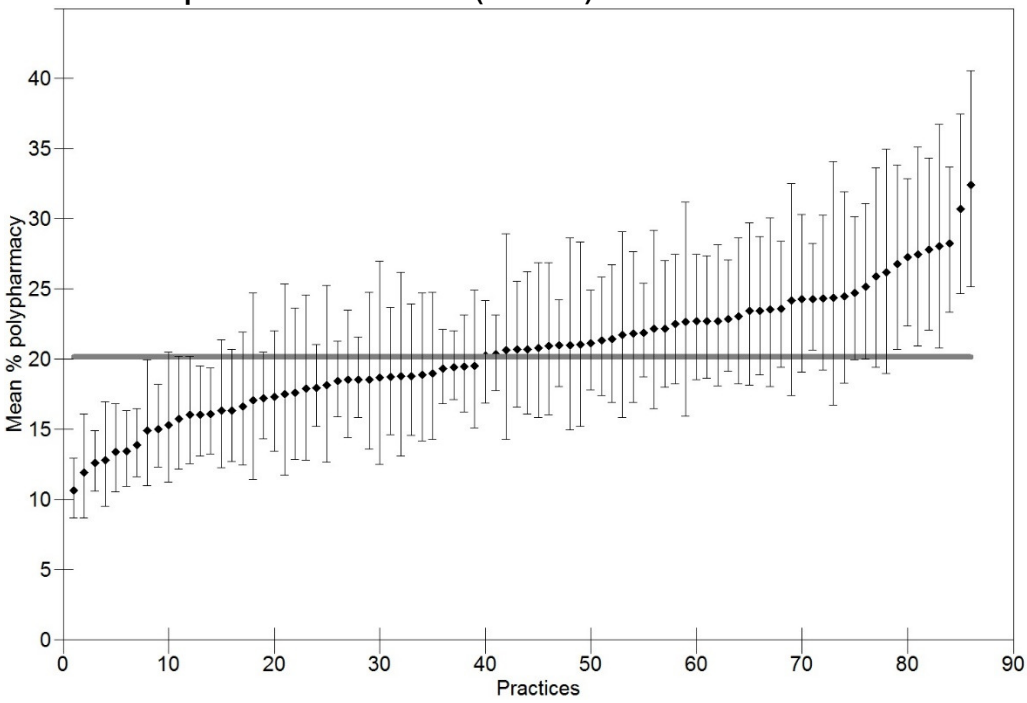
** Number of registered patients; small:1819-3408, medium: 3433-6056, large: 6059-15300*

† Estimated by counting the number of patients living in a low socioeconomic status (SES) neighborhood divided by the total practice population for whom SES information was available

‡ The pharmacies that supplied data to Foundation for Pharmaceutical Statistics (SFK) and Netherlands Institute for Health Services Research (NIVEL)

§ Type F electronic medical record software type was not included in the multilevel models since only one practice with one patient of the study population used this type.

Figure 1. The adjusted average polypharmacy prevalence per practice after accounting for differences in patient characteristics (model 2).



Note: N=44,917 patients in 86 general practices. The thick horizontal grey line at 20.1% represents the overall adjusted proportion of patients with polypharmacy. The black dotted line represents the estimated average proportions of patients with polypharmacy in each practice. The error bars represent the 95% confidence interval around the estimate of that practice.

Table 3. The association between patient and practice related variables and polypharmacy, and the inter-practice variance in proportion patients with polypharmacy with multilevel multivariate regression modeling.

	Model 1			Model 2			Model 3		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Fixed effects									
Patient characteristics									
Gender (men/women)	0.81	0.77-0.85	<0.001	1.01	0.95-1.06	0.819	1.01	0.95-1.06	0.819
Age groups:									
55-59 years	Ref.			Ref.			Ref.		
60-64 years	1.16	1.06-1.26	0.001	1.08	0.98-1.19	0.118	1.08	0.98-1.18	0.120
65-69 years	1.57	1.44-1.71	<0.001	1.39	1.26-1.52	<0.001	1.39	1.26-1.52	<0.001
70-74 years	1.85	1.69-2.02	<0.001	1.60	1.45-1.76	<0.001	1.60	1.45-1.76	<0.001
75-79 years	2.26	2.06-2.47	<0.001	1.94	1.75-2.15	<0.001	1.94	1.75-2.15	<0.001
80-84 years	2.52	2.27-2.78	<0.001	2.08	1.86-2.34	<0.001	2.08	1.86-2.34	<0.001
≥ 85 years	2.96	2.66-3.31	<0.001	2.44	2.15-2.77	<0.001	2.44	2.15-2.77	<0.001
SES categories									
High	Ref.			Ref.			Ref.		
Medium	1.15	1.05-1.26	0.003	1.12	1.01-1.24	0.028	1.10	1.00-1.22	0.061
Low	1.26	1.12-1.41	<0.001	1.20	1.05-1.36	0.005	1.14	1.00-1.30	0.042
Number of chronic conditions									
0-1 conditions	Ref.			Ref.			Ref.		
2-4 conditions	7.26	6.80-7.76	<0.001	1.37	1.24-1.51	<0.001	1.37	1.24-1.51	<0.001
≥ 5 conditions	36.4	32.8-40.3	<0.001	0.94	0.77-1.15	0.525	0.94	0.77-1.15	0.527
Type of chronic conditions									
HIV/AIDS	-	-	-	1.25	0.37-4.25	0.130	1.24	0.36-4.19	0.734
Cancer	-	-	-	1.31	1.22-1.41	<0.001	1.31	1.22-1.41	<0.001
Visual disorder	-	-	-	1.14	1.05-1.24	0.002	1.14	1.05-1.24	0.002
Hearing disorder	-	-	-	1.11	1.01-1.21	0.032	1.11	1.01-1.22	0.029
Congenital cardiovascular anomaly	-	-	-	1.88	1.13-3.13	0.014	1.89	1.14-3.14	0.014
Heart valve disorder	-	-	-	2.20	1.85-2.60	<0.001	2.19	1.85-2.60	<0.001
Heart failure	-	-	-	5.25	4.59-6.00	<0.001	5.25	4.59-6.01	<0.001
Coronary artery disease	-	-	-	6.50	6.02-7.02	<0.001	6.51	6.03-7.03	<0.001
Cardiac dysrhythmia	-	-	-	3.06	2.77-3.38	<0.001	3.06	2.77-3.38	<0.001
Hypertension	-	-	-	2.88	2.70-3.08	<0.001	2.89	2.71-3.08	<0.001
Stroke	-	-	-	3.22	2.88-3.60	<0.001	3.22	2.88-3.60	<0.001
Rheumatoid arthritis	-	-	-	3.51	3.06-4.03	<0.001	3.52	3.07-4.04	<0.001
Osteoarthritis	-	-	-	1.18	1.10-1.27	<0.001	1.18	1.10-1.27	<0.001
Chronic back or neck disorder	-	-	-	1.63	1.50-1.79	<0.001	1.63	1.49-1.78	<0.001

Table 3. (continued).

	Model 1			Model 2			Model 3		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Osteoporosis	-	-	-	2.20	1.99-2.43	<0.001	2.20	1.99-2.43	<0.001
Parkinson's disease	-	-	-	2.77	2.13-3.58	<0.001	2.77	2.14-3.59	<0.001
Epilepsy	-	-	-	2.04	1.65-2.52	<0.001	2.04	1.67-2.49	<0.001
Migraine	-	-	-	1.49	1.18-1.87	<0.001	1.49	1.19-1.87	<0.001
Chronic alcohol abuse	-	-	-	2.18	1.67-2.86	<0.001	2.17	1.66-2.84	<0.001
Dementia incl. Alzheimer's disease	-	-	-	1.89	1.55-2.31	<0.001	1.89	1.55-2.31	<0.001
Schizophrenia	-	-	-	3.96	2.47-6.36	<0.001	3.94	2.45-6.34	<0.001
Depression and psychosis	-	-	-	2.71	2.41-3.05	<0.001	2.71	2.41-3.05	<0.001
Anxiety disorder	-	-	-	2.06	1.73-2.45	<0.001	2.06	1.73-2.45	<0.001
Neuraesthenia/surmenage/burn-out	-	-	-	0.85	0.64-1.13	0.159	0.86	0.64-1.14	0.281
Personality disorder	-	-	-	2.17	1.53-3.08	<0.001	2.16	1.52-3.07	<0.001
Intellectual disability	-	-	-	1.76	1.01-3.08	0.048	1.75	1.00-3.07	0.049
COPD	-	-	-	2.46	2.26-2.68	<0.001	2.46	2.26-2.68	<0.001
Asthma	-	-	-	1.82	1.66-2.01	<0.001	1.82	1.66-2.01	<0.001
Diabetes Mellitus	-	-	-	4.70	4.38-5.04	<0.001	4.69	4.37-5.04	<0.001
Practice (population) characteristics									
Proportion practice population with multimorbidity *†	-	-	-	-	-	-	1.06	0.95-1.18	0.301
Practice location (urbanization)									
(Very) strong	-	-	-	-	-	-	Ref.		
Moderate	-	-	-	-	-	-	0.78	0.64-0.94	0.008
Little or not	-	-	-	-	-	-	0.81	0.68-0.97	0.025
Random effects									
Practice variance component (SE)	0.066 (0.013)			0.095 (0.018)			0.081 (0.016)		
Mean % polypharmacy	21.4%			20.1%			19.8%		
95% CI polypharmacy ‡	14.1% – 31.0%			12.1% - 31.6%			12.4% - 30.1%		
% variance explained regarding the previous model §	-			-43.9%			14.7%		

Note: Total N=44,917 patients in 86 practices. All models were adjusted for the practice's EMR software type. OR= odds ratio; CI= confidence interval; SE= standard error

** These proportions are based on information of the total practice population*

† Continuous variables

‡ The 95% coverage interval. The range indicates the practices' difference in polypharmacy prevalence

§ This is the proportion variance in polypharmacy between practices explained by including explanatory variables (e.g.. (Varpracticemodel1- Varpracticemodel2)/ Varpracticemodel1)

DISCUSSION

Although polypharmacy is common in primary care, this is one of the first studies examining the variation in polypharmacy prevalence between general practices. It was shown that after accounting for differences in patient and practice characteristics, practice variation existed in the polypharmacy rate between practices (factor 2.4). Higher age and most prevalent chronic conditions were highly positively associated with polypharmacy, and to a lesser extent, a lower SES. Further, practices located in lower urbanized areas had a lower odds ratio of polypharmacy than (very) strong urbanized located practices.

One study from 1995 examined inter-practice variation in relation to polypharmacy rates in general practices[21]. They showed lower rates of polypharmacy and more inter-practice variation, that is, a six fold variation. The discrepancy in findings might be due to the increasing prevalence of polypharmacy in recent years[13] or to changes in regulation and the rise in the development of disease guidelines[35, 36]. Furthermore, the introduction of electronic health record systems, electronic prescription systems, and guidelines that recommend uniformity in recording are also likely to contribute to reduced variation between practices[37].
Recently conducted studies on polypharmacy found prevalence rates comparable with our findings[2, 14]. In accordance with our hypothesis, and similar with other studies, we found that higher age and number of chronic conditions were highly positively associated with polypharmacy[2, 6, 13-15, 38]. It was also found that the type of chronic conditions was associated with the number of medications[2, 38]. Our current study underlined that especially the type of diseases, rather than the number of diseases, was related to the number of medications prescribed. The strong association between the number of conditions and polypharmacy decreased when including the type of chronic conditions. Remarkably, an increase in the number of prevalent chronic conditions is not directly accompanied by an increase in prescribed medications. In patients with five or more conditions, it seems that other factors start to play an important role, for instance, interactions between medications, other treatment options like surgery, or perhaps maintaining the status quo[9]. Some diseases are associated with a high number of prescribed medications[2, 38], and especially as -not unlikely in this age group- other diseases are involved as well, this could lead to several eligible treatment options and practice variation in the number of prescribed medications. Nevertheless, after accounting for the type of chronic conditions, still considerable variation between practices remained. The finding that practices located in the lowest and moderately urbanized areas had a significantly lower odds ratio of polypharmacy than very strong urbanized located practices cannot be confirmed in literature. Guthrie et al[20] found that practices located in moderately urbanized areas were more likely to have patients with a high-risk prescription than practices in primary cities; however, the clinical significance of the associations were marginal[20]. In contrary to our hypothesis, practice size did not

significantly affect polypharmacy prevalence as had been shown in other studies. Yet, in these studies, those factors could hardly explain any variance in prescribing (high risk) medication[18, 20].

Strengths of the study are the number of data; 86 practices with, on average, 500 older patients, which contributes to stable and robust multilevel models. A second strength concerned the analyses of actually distributed medications from the pharmacist to the patient instead of just prescription data. A possible limitation is that due to the fact that not all pharmacies agreed to share their data with the NIVEL-PCD, the study population covered a subpopulation of the total general practice sample. Nevertheless, it was found that the studied patients were comparable as regards the mean age and gender with a larger sample of eligible patients only available in NIVEL-PCD. Further, the proportion of patients with polypharmacy may be slightly overestimated as patients with one or two prescriptions were less likely to be included in the analyses because of the applied linkage method. Yet, the majority of the study population (90%) did receive more than two prescriptions, and as it applies to all practices in the same order, it is not likely to affect the results of our main question, namely, practice variation. The identified variation in polypharmacy prevalence might not only be due to the GPs, or physicians working in the general practice. Our dispensed medication data could also hold medications prescribed by medical specialists. Besides, also the pharmacist could have a role in the medications dispensed as he or she checks whether the patients' prescribed medications can be combined.

Because evidence for effective treatment is mostly gathered in younger adults without multimorbidity, it seems logical that for older patients with multiple chronic conditions, physicians more often rely on their own experiences and reasoning when prescribing medications. This is not necessarily worrisome if it is justified, for instance, when accounting for the patient's preferences and priorities[39]. However, because considerable variation between practices existed after accounting for differences in patient and practice characteristics, the results indicate that physicians from different practices have different prescribing behaviors, and it suggests that there might be professional uncertainty about the best treatment. However, next to the GP, also the medical specialist and pharmacist play an important role in medication therapy management. It is likely that part of the unexplained variation is due to pharmacy-related factors or by factors that indicate the level of cooperation between the GP and pharmacist. Several strategies and activities exist to reduce unnecessary medication use, involving different health care professionals such as the GP and pharmacist[29, 40-46]. For instance, when contemplating on complex patients and medication combinations, this could turn differences in management views into a common view. It seems valuable to further investigate possible explanations for the variance in polypharmacy prevalence, such as

differences in physician-related characteristics, such as their clinical experience, and in the level of cooperation between the various professionals involved in medication prescribing.

In conclusion, because numerous inter-practice variation in polypharmacy prevalence exist, attention for medication management is important, especially in complex older patients with multiple chronic conditions. Physician initiatives to achieve a more shared vision about the best therapeutic treatment add to the patient's value of care.

References:

1. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43.
2. Payne RA, Avery AJ, Duerden M, Saunders CL, Simpson CR, Abel GA. Prevalence of polypharmacy in a Scottish primary care population. *Eur J Clin Pharmacol*. 2014;70(5):575-781.
3. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA*. 2005;294(6):716-724.
4. Tinetti ME, Bogardus ST, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med*. 2004;351:2870-2874.
5. Fried TR, Tinetti ME, Iannone L. Primary care clinicans' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med*. 2011;171(1):75-80.
6. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. 2007;5(4):345-351.
7. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. *Br J Clin Pharmacol*. 2014;77(6):1073-1082.
8. Holmes HM, Luo R, Kuo YF, Baillargeon J, Goodwin JS. Association of potentially inappropriate medication use with patient and prescriber characteristics in Medicare Part D. *Pharmacoepidemiol Drug Saf*. 2013;22(7):728-734.
9. Sinnott C, Hugh SM, Boyce MB, Bradley CP. What to give the patient who has everything? A qualitative study of prescribing for multimorbidity in primary care. *Br J Gen Pract*. 2015;65(632):e184-e191.
10. Frank C, Weir E. Deprescribing for older patients. *CMAJ*. 2014;186(18):1369-1376.
11. De Jong JD. Explaining medical practice variation, Social organization and institutional mechanisms [*dissertation*]. Utrecht: Utrecht University. 2008.
12. Ohlsson H. Understanding therapeutic traditions in a multilevel framework - new methodological approaches [*dissertation*]. Lund University. 2009.
13. Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. *BMC Clin Pharmacol*. 2010;10:16.
14. Nobili A, Franchi C, Pasina L, Tettamanti M, Baviera M, Monesi L, et al. Drug utilization and polypharmacy in an Italian elderly population: the EPIFARM-Elderly Project. *Pharmacoepidemiol Drug Saf*. 2011;20(5):488-496.
15. Skoog J, Midlov P, Beckman A, Sundquist J, Halling A. Drugs prescribed by general practitioners according to age, gender and socioeconomic status after adjustment for multimorbidity level. *BMC Fam Pract*. 2014;15:183.
16. Van Dijk L, de Jong JD, Westert GP, de Bakker DH. Variation in formulary adherence in general practice over time (2003-2007). *Fam Pract*. 2011;28(6):624-631.
17. Stewart RE, Vroegop S, Kamps GB, van der Werf GT, Meyboom-de Jong B. Factors influencing adherence to guidelines in general practice. *Int J of Technol Assess Health Care*. 2003;19(3):546-554.
18. Davis P, Gribben B. Rational prescribing and interpractitioner variation. A multilevel approach. *Int J of Technol Assess Health Care*. 1995;11(3):428-442.

19. Cahir C, Fahey T, Teljeur C, Bennet K. Prescriber variation in potentially inappropriate prescribing in older populations in Ireland. *BMC Fam Pract*. 2014;15:59.
20. Guthrie B, McCowan C, Davey P, Simpson CR, Dreischulte T, Barnett K. High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. *BMJ*. 2011;342:d3514.
21. Bjerrum L, Sogaard J, Hallas J, Kragstrup J. Polypharmacy in general practice: differences between practitioners. *Br J Gen Pract*. 1999;49(440):195-198.
22. Van den Dungen C, Hoeymans N, Boshuizen HC, van den Akker M, Biermans MC, van Boven K, et al. The influence of population characteristics on variation in general practice based morbidity estimations. *BMC public health*. 2011;11:887.
23. Van den Dungen C, Hoeymans N, van den Akker M, Biermans MC, van Boven K, Joosten JH, et al. Do practice characteristics explain differences in morbidity estimates between electronic health record based general practice registration networks? *BMC Fam Pract*. 2014;15:176.
24. Verheij RA. Over NIVEL Zorgregistraties: geschiedenis en achtergrond. Uit: *NIVEL Zorgregistraties eerste lijn*. 2013. Accessed 25 June 2015. [www.nivel.nl/node/3464].
25. Griens AMGF, Janssen JM, Kroon JDL, Lukaart JS, Van der Vaart RJ. SFK Facts and Figures 2014. The Hague: *Foundation for Pharmaceutical Statistics* (SFK), 2014.
26. Mossialos E, Wenzl M, Osborn R, Anderson C. International Profiles of Health Care Systems, 2014. New York: *The Commonwealth fund*, 2015.
27. Hek K, Kroon JDL, Janssen JM, van Dijk L. Verantwoording cijfers apotheken. Uit: *NIVEL Zorgregistraties eerste lijn*. 2013. Accessed 19 June 2015. [www.nivel.nl/node/3531].
28. Florentinus SR, Souverein PC, Griens FA, Groenewegen PP, Leufkens HG, Heerdink ER. Linking community pharmacy dispensing data to prescribing data of general practitioners. B*MC Med Inform Decis Mak*. 2006;6:18.
29. NHG. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: *Nederlands Huisartsen Genootschap*, 2012.
30. Knol F, Boelhouwer J, Veldheer V. Statusontwikkeling van wijken in Nederland 1998-2010. Den Haag: *Sociaal en Cultureel Planbureau*, 2012.
31. Doekhie KD, de Veer AJE, Rademakers JJDJM, Schellevis FG, Francke AL. NIVEL Overzichtstudies- ouderen van de toekomst. Utrecht: *NIVEL*, 2014.
32. Sinnige J, Korevaar JC, Westert GP, Spreeuwenberg P, Schellevis FG, Braspenning JC. Multimorbidity patterns in a primary care population aged 55 years and over. *Fam Pract*. 2015. 352(5):505-513.
33. Nielen M, Spronk I, Davids R, Korevaar J, Poos R, Hoeymans N, et al. A new method for estimating morbidity rates on electronic health records from general practitioners. *Manuscript submitted for publication.* 2015.
34. Snijders TAB, Bosker RJ. Multilevel Analysis: An introduction to Basic and Advanced Multilevel Modeling (2nd edn). *Sage Publishers*: London, 2012.
35. Grol R. Development of guidelines for general practice care. *Br J Gen Pract*. 1993;43:146-151.
36. Ohlsson H, Vervloet M, van Dijk L. Practice variation in a longitudinal perspective: a multilevel analysis of the prescription of simvastatin in general practices between 2003 and 2009. *Eur J Clin Pharmacol*. 2011;67(12):1205-1211.
37. NHG. Richtlijn Adequate dossiervorming met het Elektronisch Patiëntendossier ADEPD. Utrecht: *Nederlands Huisartsen Genootschap,* 2009.

38. Vyas A, Pan X, Sambamoorthi U. Chronic condition clusters and polypharmacy among adults. *Int J Family Med*. 2012.
39. Milton JC, Hill-Smith I, Jackson SH. Prescribing for older people. *BMJ*. 2008;336(7644):606-609.
40. Task Force on Medicines Partnership and The National Collaborative Medicine Management Services Programme. Room for review. A guide to medication review: the agenda for patients, practitioners and managers. *London: Medicines Partnership*, 2002.
41. Van Dijk L, Barnhoorn H, de Bakker D. Het Farmaco Therapie Overleg in 1999: stand van zaken en effecten op voorschrijven. Utrecht: *NIVEL*. 2001.
42. Florentinus SR, van Hulten R, Kloth ME, Heerdink ER, Griens AM, Leufkens HG, et al. The effect of pharmacotherapy audit meetings on early new drug prescribing by general practitioners. *Ann Pharmacother*. 2007;41(2):319-324.
43. Osborn R, Moulds D, Squires D, Doty MM, Anderson C. International survey of older adults finds shortcomings in access, coordination, and patient-centered care. *Health Aff (Milwood)*. 2014;33(12):2247-2255.
44. Muijrers PE, Grol RP, Sijbrandij J, Janknegt R, Knottnerus JA. Differences in prescribing between GPs: impact of the cooperation with pharmacists and impact of visits from pharmaceutical industry representatives. *Fam Pract*. 2005;22(6):624-630.
45. Teichert M, van der Aalst A, de Wit H, Stroo M, De Smet PA. How useful are prescribing indicators based on the DU90% method to distinguish the quality of prescribing between pharmacotherapy audit meetings with different levels of functioning? *Eur J Clin Pharmacol*. 2007;63(12):1171-1177.
46. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Hughes C. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2014;10:CD008165.

Chapter 5

Medication management strategy for older people with polypharmacy in general practice: a qualitative study on prescribing behavior in primary care

J. Sinnige
J.C. Korevaar
J. van Lieshout
G.P. Westert
F.G. Schellevis
J.C. Braspenning

The British Journal of General Practice. 2016;66(649):e540-e551

ABSTRACT

Background: For older patients with polypharmacy, medication management is a process of careful deliberation that needs periodic adjustment based on treatment effects and changing conditions. Because of the heterogeneity of the patient group, and limited applicability of current guidelines, it is difficult for GPs to build up a routine.

Aim: To gain insight into GPs' medication management strategies for patients with polypharmacy, and to explore the GPs' perspectives and needs on decision-making support to facilitate this medication management.

Design and setting: Two focus group meetings with Dutch GPs, discussing four clinical vignettes of patients with multimorbidity and polypharmacy.

Method: Questions about medication management of the vignettes were answered individually; the strategy chosen in each case was discussed in a plenary session. Analysis followed a Framework approach.

Results: In total, 12 GPs described a similar strategy regarding the patients' medication management: Defining treatment goals; determining primary goals; and adjusting medications based on the treatment effect, GPs' and patients' preferences, and patient characteristics. There was variation in the execution of this strategy between the GPs. The GPs would like to discuss their choices with other professionals and they valued structured medication reviews with the patient, as well as quick and practical support tools that work on demand.

Conclusions: To facilitate decision making, a more extensive and structured collaboration between health care professionals is desired, as well as support to execute structured medication reviews with eligible patients, and some on-demand tools for individual consultations.

INTRODUCTION

An ageing population means GPs increasingly manage older patients with multiple chronic conditions (that is, multimorbidity)[1-3]. These patients are often recommended to use multiple different medications at several times of the day. The chronic use of at least five medications is also called 'polypharmacy'[4, 5]. In a recent study, it was found that the proportion of older patients with polypharmacy varied, by a factor of 2.4, between general practices after accounting for differences in the patient and practice population[6]. This suggests that medication management, the process of monitoring and evaluating the patient's prescribed medications, differs between GPs. Both multimorbidity and polypharmacy are associated with a range of adverse health outcomes, for instance, a lower quality of life, more adverse drug reactions, and higher rates of unplanned hospitalization[5, 7, 8]. Therefore, in older patients with polypharmacy, attention to appropriate medication prescribing is of major importance.

GPs in the Netherlands are searching for appropriate polypharmacy for older patients to help optimize prescriptions[9], while taking into account the best evidence along with patient perspectives; but this is often complex. It concerns a heterogeneous patient group as regards the combination in types and severity of diseases[10]. Each patient also has their own characteristics (age, prognosis, cognitive ability, and preferences) to be taken into account[11, 12]. Due to changes in conditions of life and treatment effects, which are likely in this patient group, periodic adjustment of the prescribed medications is necessary. Unfortunately, due to the single-disease focus of most clinical practice guidelines (CPGs), it is not always possible to adopt the recommendations on medication prescribing in patients with multimorbidity[13-16]. GPs have to find a balance between the risks and benefits of adhering to the CPGs and providing patient-centered care[12, 15]. In daily practice, GPs and patients often decide together which prescribing option to start with, and GPs often rely on their own experience when changing or stopping a medication prescription[17, 18].

Considering the limited applicability of CPGs and the heterogeneous patient group, little is known of how GPs assess the benefits and harms of the available treatment options. Furthermore, it remains unclear how GPs make decisions in medication management, and by what kind of factors this management is influenced. Therefore, this study aims to gain insight into the GPs' medication management strategy for older patients with polypharmacy, and to explore the GPs' perspectives, needs, and ideas on decision-making support to facilitate medication management for these patients.

METHODS

Design

Two focus groups meetings with experienced GPs were organized. Local trainers were motivated to create more awareness among the trainees on polypharmacy and two meetings were organized within their training program. All GPs participated voluntarily, being informed that anonymity and confidentiality were ensured; the discussion was audio-recorded. The meeting started with an individual written medication review of clinical case vignettes. A senior GP who lectured the GP-trainers moderated the meetings assisted by two researchers. The topic guide covered items on the medication management strategy, the accomplishment of the strategy, impact factors (sex, age, lifestyle, social context), and support tools.

Clinical case vignettes

Each focus group meeting started with an individual assignment for the GPs; reviewing medication management of four clinical case vignettes covered in a survey. The vignettes are described in **Appendices 5.1–5.4**, accompanied with possible treatment considerations, based on Dutch CPGs. The vignettes described patients (aged 68–84 years) diagnosed with multiple, highly prevalent chronic diseases, often part of a cluster of diseases[10]. The patients used multiple medications, some of which can influence clinical functions, such as impaired renal function due to NSAIDs, or furosemide and hyponatremia[19, 20], or can induce symptoms (for example, dipyridamole and headache). The vignettes varied as regards to the safety of the combination of the medications, patient's sex, age, lifestyle, and social context. The questions accompanying the vignettes covered treatment goals, an appraisal of the patient's prescribed medications, and the possibility of consulting another health care professional. The vignettes were developed by two of the authors and were validated by two additional practicing GP-researchers.

Analysis

A Framework approach[21] was used by defining themes a priori, in order to facilitate the plenary session and to focus on the research aims. The themes were integrated into the clinical vignette survey, and concerned 'patient complexity' and 'treatment goals/strategy', as these concepts were both considered as influencing GPs' management[12, 18, 22]. Concerning decision support, no a priori themes were defined. After the first meeting, the audio-tape was transcribed verbatim. The transcript was case and thematically coded by one researcher and quotes were classified into the two themes, if possible, or new themes were reported. If new themes emerged, they were discussed during the second meeting. The second meeting added no new themes and the course was comparable with the first meeting. The data indexed into the themes were

checked by a second researcher and, in any case of disagreement, the two researchers were in discussion until consensus was reached.

RESULTS

Participants and group dynamics

A total of 12 GPs participated in two focus groups, each lasting around 75 minutes. All the GPs worked in the eastern or southern part of the Netherlands, and had, on average, 24.8 years of work experience (**Table 1**). The plenary sessions were dynamic. The GPs were enthusiastic, eager to hear about the considerations made by their peers, and the meeting was considered useful:

> *'It turns out (again) that we should discuss these patients not on our own, but in a team, as it yields more [information] than you anticipate.' (GP5)*

Table 1. Characteristics of the GPs participating in the focus groups (total *N*=12).

		N*
Sex		12
Male, %	66.7	8
Mean age, years [range]	56.3 [46-63]	12
Mean years of work experience as a GP [range]	24.8 [10-35]	12
Mean days working as a GP [range]†	4.1 [3-5]	11
Practice holder†		11
Yes, %	100.0	11
Practice type†		11
Solo	18.2	2
Duo	36.4	4
Group	45.5	5
Practice with above average number of older patients (≥65 years)†‡		10
Yes	30.0	3
No	70.0	7
Practice including a pharmacy†		11
Yes	18.2	2
No	81.8	9
Mean no. of cooperating pharmacies [range]†	3.2 [1-5]	9
Frequency of organized meetings with pharmacists†		9
Monthly	44.5	4
Bimonthly	22.2	2
1-2 times a year	22.2	2
Never	11.1	1

** For some questions, there was missing data*

† The moderator also participated in one meeting (and completed the clinical vignette survey) but was not active as a GP in a practice any more (since 1 year). Therefore, for applying the background questions the total N is 11.

‡ Based on the question, 'On average around 16% of the Dutch population is 65 years and older. Do you think that more than 16% of your practice population is 65 years or older?'

GPs' medication management strategy

All GPs described a quite similar medication management strategy. First, treatment goals were defined and prioritized, usually together with the patient. Second, the goals that were considered the primary concern in treatment were determined, and the focus of the current consultation was agreed. Mostly, primary goals were the reason for the encounter, or were regarded as important to prevent damage:

> *'I think you should treat that first, this man's complaints [case 4]. He is currently in a lot of pain.' (GP2)*

> *'In my opinion [treating] the blood pressure is always the most important because the lower the blood pressure, the lower the chance for a CVA, TIA, or renal failure. That is my consideration.' (GP5)*

Third, adjustments were made in the patient's prescribed medications, while considering the formulated primary goal(s). Often, one or two adjustments were suggested immediately:

> *'I don't see, I don't think the blood sugar level is too low [case 3], thus you could change a lot but I would start with [treating] the heart failure … If the HbA1c still decreases, then we could consider it [adjusting metformin].' (GP11)*

Accomplishment of the strategy

Although a similar strategy for polypharmacy was described, there was variation between GPs in the actual performance. There was variation in the (number of) treatment goals formulated for the patient, and the number of proposed primary goals; there was a focus on addressing several goals simultaneously versus a 'step-by-step' approach. Further, there was variation as regards focusing on optimizing clinical values by referring to targets described in CPGs, or focusing on the reason for an encounter. As a result, the proposed adjustments in the cases' prescribed medications varied (**Figures 1–4**). In **Box 1** noteworthy findings per vignette are given, accompanied by statements made from GPs. The GPs expressed that work experience facilitates the decision-making process. Nevertheless, they seemed indecisive about the best approach; they repeatedly declared that they needed to search for information (for example, reference values, medication dosages, potential side effects), and were interested in the approach of other GPs. Besides, several prescribing options seemed possible according to the GPs. Yet, consulting a pharmacist or medical specialist was rarely considered, as they wanted to optimize the patient's condition themselves first. Only if the patient's condition did not improve, would they be likely to deliberate with a medical specialist.

Figure 1. Case 1 (Appendix 5.1): number of GPs that reported adjusting the particular prescribed medication in the case vignettes. 'Adjust' can indicate changing the dosage or stopping the prescribed medication.

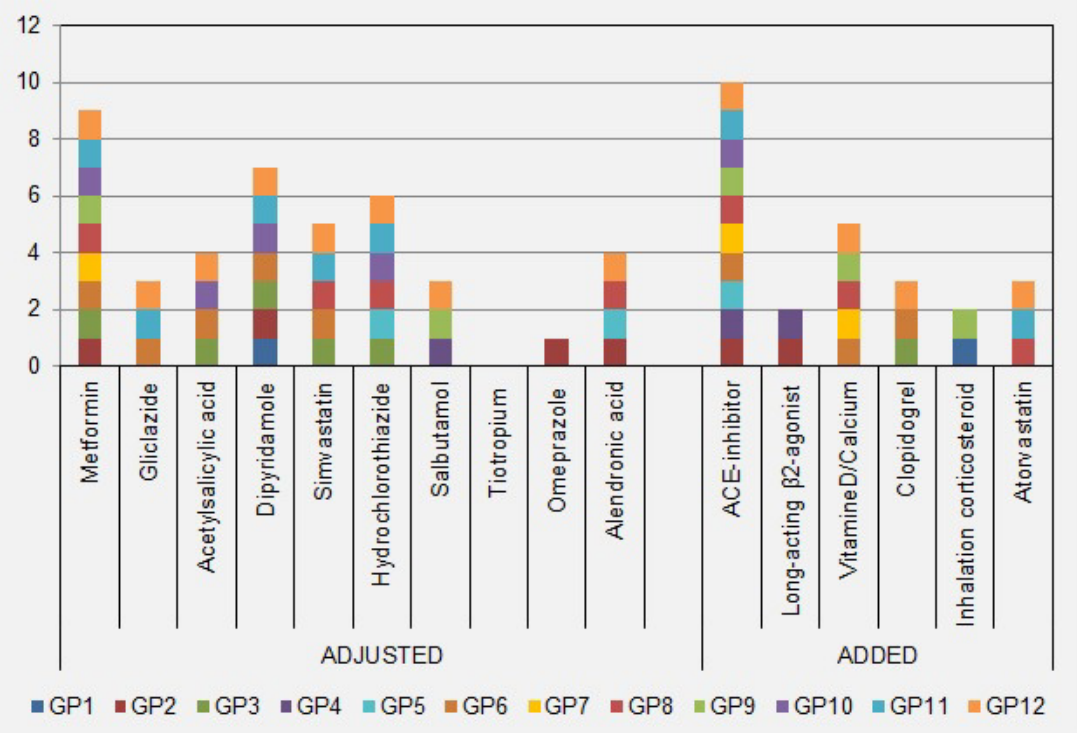


Figure 2. Case 2 (Appendix 5.2): number of GPs that reported adjusting the particular prescribed medication in the case vignettes. 'Adjust' can indicate changing the dosage or stopping the prescribed medication.

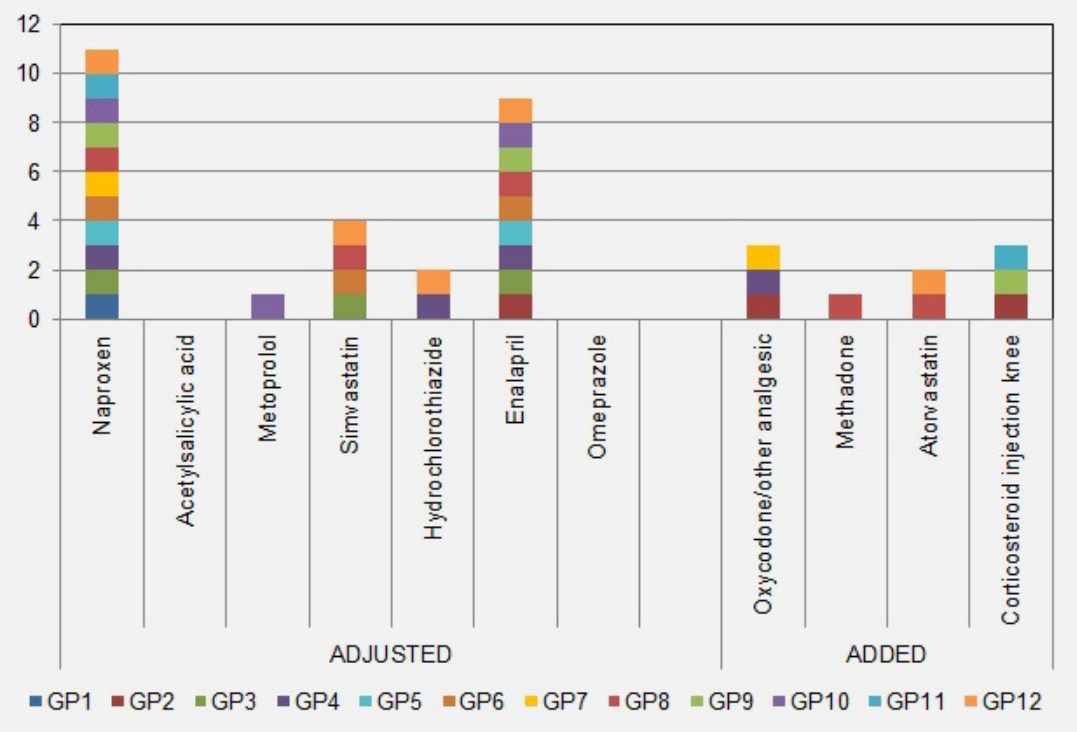


Figure 3. Case 3 (Appendix 5.3): number of GPs that reported adjusting the particular prescribed medication in the case vignettes. 'Adjust' can indicate changing the dosage or stopping the prescribed medication.

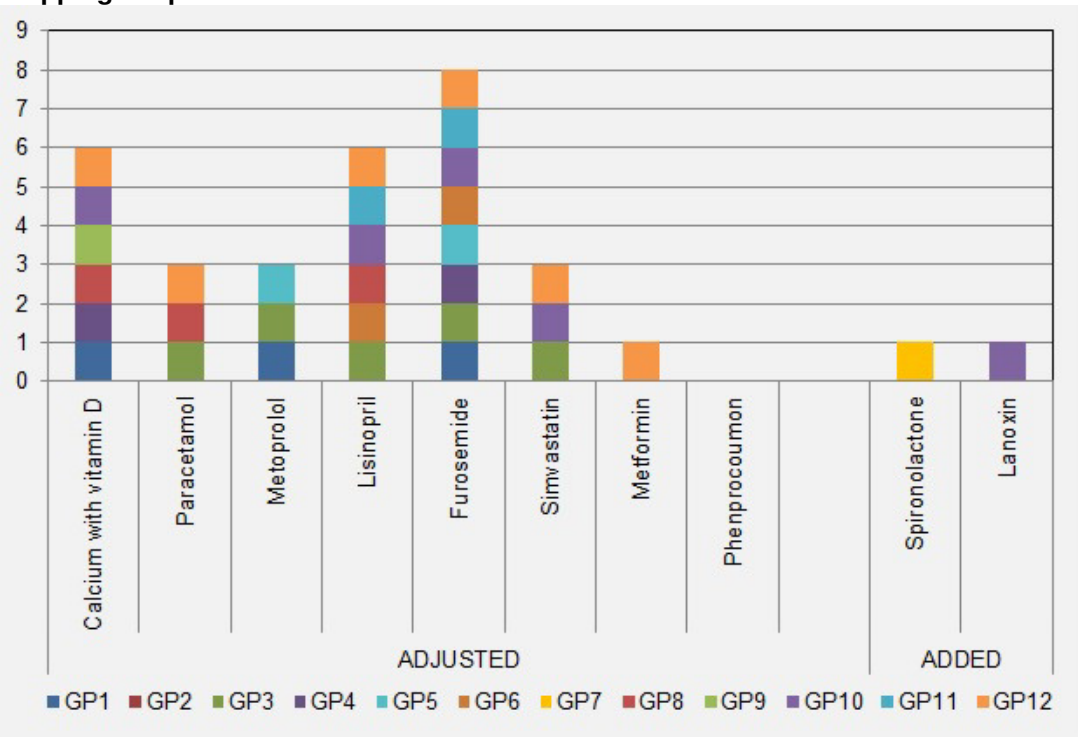
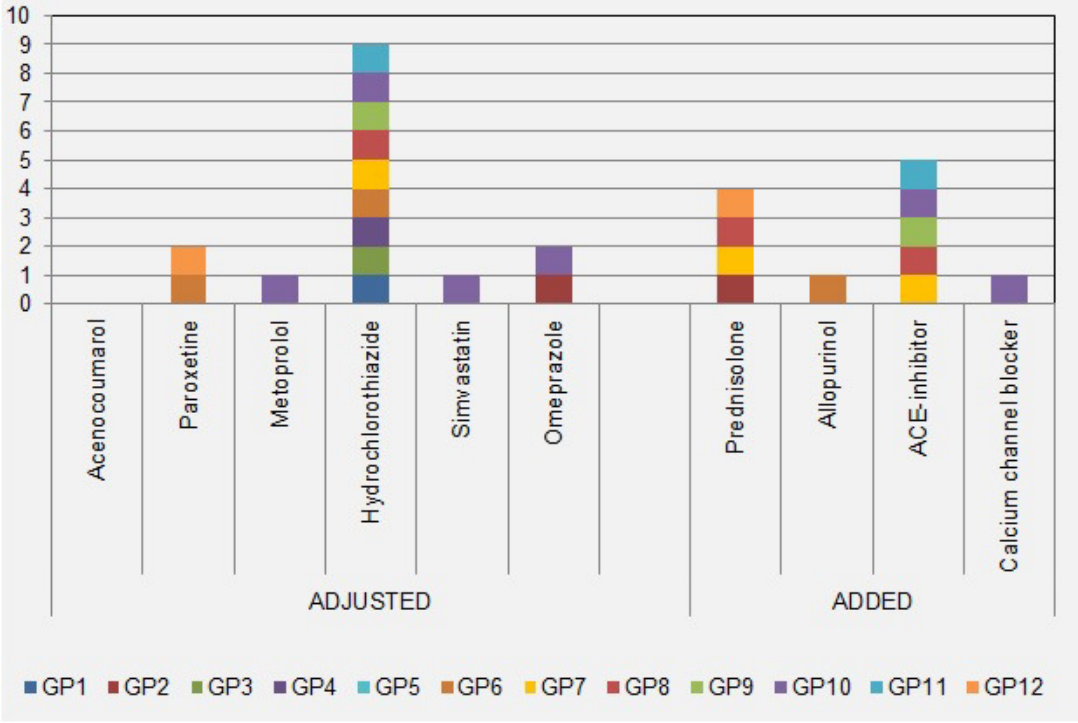


Figure 4. Case 4 (Appendix 5.4): number of GPs that reported adjusting the particular prescribed medication in the case vignettes. Adjust' can indicate changing the dosage or stopping the prescribed medication.



Factors influencing the medication management process

The patient's age, vitality, prognosis/ life expectancy, and quality of life were mentioned as factors influencing medication management. For instance, the patient's age influenced the GP's adherence to CPG recommendations. GPs accepted less optimal clinical values if the patient's quality of life was at stake:

> *'[If the patient was 85 years old] I would be more flexible about the blood pressure. That it will not result in, that he [case 2] falls or gets dizzy, or falls from a chair. I rather want him to be active with a higher blood pressure, than inactive with a lower pressure.' (GP9)*

Furthermore, the patient's social context was considered important for the focus of the treatment, as well as their perspectives, wishes, and preferences on the proposed treatment:

> *'I think that you could have an interesting talk with her [case 3] about what she aims for, and how frail she is.' (GP7)*

Regarding medication-related factors, the number of prescribed medications and the dosage, together with the combination of diseases, contributed to the complexity in management. When deliberating with the patient on potential medication adjustments, GPs sometimes hesitated to change or stop a prescribed medication. For instance, when medications were prescribed in their current dosage for a long period, or when it concerned medications prescribed by a medical specialist:

> *'It is always a dilemma, a tense situation [adjusting medications]. We know that many hospital admissions are caused by medication … "errors" is a strong word, but surely due to failures in adequate medication. But we do know that stopping everything at once will also become counterproductive. Thus, that is really something to consider.' (GP1)*

Decision-making support tools

The GPs expressed that it was hard to think about appropriate support tools because of the heterogeneity of the patients. Tools regarded valuable by some GPs were characterized as practical and quick to use, such as the CHA2DS2-VASc score for stroke risk assessment[23], or the CVD risk assessment tool[24]. Tools providing insight into the practices' frail older population were also mentioned. Some existing tools incorporated in the GPs' electronic medical record (EMR) system to check applicable CPGs lacked the GPs' preferred ability to use it only when they needed it -to use it on demand. According to some GPs:

'It would be nice if you can do that on demand. That there would be a button in your system which would automatically compare the medications and lab results, and then would report "the advice would be to …" But only when you press the button, and not that it goes "plop, plop" every time.' (GP6)

Overall, two main options for support were valued. The first concerned meetings with GPs or pharmacists to discuss patients with complex problems, as a check of their expertise, and to exchange ideas and information around medication management decision making. About half of the GPs reported having meetings with a pharmacist at least bi-monthly, but only a few already discussed the older patients in multidisciplinary teams:

'It is not such a bad idea to do [talking about complex patients], and to discuss them together, like we are doing right now. When doing so, you come up with new ideas sooner, like, I should pay more attention to those factors.' (GP10)

The second option concerned medication reviews with the patient[25], executed during an annually extensive consultation. Some GPs stated that agreements with a pharmacist were made to perform a medication review, and a few participated in a program focusing on managing the frail older patient, that included a medication review. Nevertheless, it seemed that the two options for support were not yet structurally performed. Perceived issues related to the execution of medication reviews were; lack of time, minimal beneficial results, and uncertainty about the patients who may be eligible for a review. Subsequently, GPs stated that the means to select these eligible patients systematically and easily were not sufficiently applicable.

DISCUSSION

Summary

Although the GPs had a similar medication management strategy, there was variation as regards the accomplishment of this strategy, due to differences in the GPs' approaches (for example, focus on clinical values versus reason for encounter, or step-by-step versus simultaneous approach). Patient- and medication-related factors influenced the medication management process. As a result, variation existed in the proposed adjustments of the patients' prescribed medications. Collaboration between GPs and pharmacists was valued as a medium to discuss patients with complex medication regimens, as well as structured medication reviews with the patient, and quick tools that work on demand.

Box 1. Findings per case vignette, accompanied by statements given from the participating GPs.

For case 1 (Appendix 5.1), it can be seen that all GPs focused on lowering blood pressure in this patient, which resulted in adding an ACE inhibitor. The variation in changes could be due to the fact that some GPs had more primary goals, whereas others had a more 'step-by-step' approach: '*I have changed a series of prescribed medications. I am not sure if I will change everything at once, but this would be my purpose*' (GP8) and '[about the fact that this GP reported far less adjustments in the medication list] *Yes, I did not want to adjust everything at the same time. I have recorded the medications which I would like to change at first place. After that you will see the patient again, and then you could focus on remaining goals. It is not very inspiring for the relationship of trust if you would say "Now we will do everything differently" after 8 years of treatment.*' (GP9)

With respect to case 2 (Appendix 5.2), nearly all GPs stated that naproxen should be stopped immediately, but not all GPs suggested alternatives for treating the patient's pain. Moreover, only some GPs mentioned pain management as a treatment goal. Furthermore, all GPs suggested focusing on lowering blood pressure, but some GPs preferred to await the effect of stopping naproxen before increasing the dosage of enalapril.

GPs considered case 3 (Appendix 5.3) a typical 'general practice patient' because their approach would be to make one or two changes, wait a few days, and then determine the effect of the changes. For this patient, there was no apparent primary treatment goal: 10 different treatment goals were reported, and most GPs focused on three or four goals. This could be due to ambiguity about some symptoms or complaints. A GP stated, '*That dizziness, we don't know the type of dizziness. I am curious about the woman's type of dizziness, I really want to know that. It hinders me.*' (GP1)

As regards case 4 (Appendix 5.4), nearly all GPs said that they would wish to stop hydrochlorothiazide because of the patient's gout attack, despite the fact that this is no longer recommended in the Dutch guidelines. Treatment goals mainly focused on pain management and lowering the blood pressure.

Strengths and limitations

Clinical vignette surveys are shown to be effective for the evaluation of treatment decisions made by GPs[29-31]. The applied study design can be seen as a major strength, because all GPs assessed identical hypothetical patients and thus provided insight into some level of variance regarding medication decision making. Further, using focus group meetings enabled GPs to contemplate the same patient, and to enquire about possible reasons for variation in their prescribing management. A limitation of this study is the inclusion of only experienced GPs, thus introducing possible bias. More specifically, GPs in

other studies mentioned lacking certain skills, or felt incompetent managing patients with multimorbidity[11, 26, 27]. Although this was not found in the present study, it was also not explicitly asked about. Also, only two meetings were organized. However, because the second meeting did not reveal any new themes, and the content of the discussion resembled the first meeting, the data-collecting process was considered saturated.

Comparison with existing literature

Contrary to the methods chosen in previous studies[11, 12, 17, 18, 22, 26, 27], this study incorporated the assessment of case vignettes based on fictitious patients into focus group sessions, which yielded information about variation in medication adjustments between GPs, as well as considerations for the choices made. This study therefore clearly showed that, for similar patients, GPs executed their medication management strategy quite differently. As far as the authors are aware, this has not been found in other studies. As to factors influencing decision making, these findings show similarities with existing literature. For instance, the findings that less stringent levels of disease control were accepted, that compromises were made between what a GP thought was best for a patient and the patient's requests, and that setting priorities in management was of importance[17, 18]. In a study by Schuling and colleagues[11], it was stated that some GPs hesitated to discuss the subject of life expectancy. This is contrary to the findings in this study, as all GPs intended to enquire about a patient's prognosis and quality of life. Luijks and colleagues[12] showed that the patient's quality of life was a main focus of GPs' professional performance, and management was adapted to personal preferences and vitality. Adhering to available CPGs has been described as not very realistic or as even unwanted in polypharmacy[11, 18, 28]. Although guideline adherence was not a main topic in these sessions, the GPs indicated that they did not always adhere to the CPGs, but they referred to CPGs as a fundamental basis for judgement.

Implications for practice

Even GPs with a lot of experience and skills perceive the need for additional support to facilitate decision making in polypharmacy. Considering the potential consequences of failure in medication management, it seems evident that decision-making support tools, such as BADRI[32], although not available in the Netherlands, are important. As evidence is available that a programmatic approach can be effective, and the availability of these support tools increases, it should be stressed that implementation strategies are needed to facilitate their usage in practice. In a systematic review on decision-making tools for multimorbidity[33], none of the available tools included a patient-centered approach, or worked on demand -components that were regarded as important by the GPs in the present study. Focusing on extensive collaboration between health care professionals seems therefore more promising as a means to facilitate medication management and to reduce possible inappropriate variation in medication prescribing. Although a few GPs

indicated they participate in multidisciplinary team meetings, there seems to be room for improvement as regards embedding these meetings structurally. Because structured meetings with GPs and pharmacists around pharmacotherapy already exist (as in pharmacotherapy audit meetings)[34, 35], these seem suitable to embed discussions around patients with complex polypharmacy. Medication reviews with patients can also facilitate medication management, but currently do not seem to be structurally performed. More knowledge is needed on the role patients can play in these reviews, especially regarding their health literacy[36]. Interventions exist that include executing a medication review, but these are not embedded nationwide. Also, acceptable software that could extract eligible patients seemed insufficiently applicable to GPs. Recently, Sinnott and colleagues[37] described a future intervention to improve medication management by combining the concept of discussing complex patients with multiple GPs, and discussing the determined results during a medication review with the patient. It seems a promising intervention; however, it does not account for the uncertainty around the potential patient group eligible for such a review pointed out by the GPs in the current study. Therefore, it is worthwhile enquiring about the group eligible for such a review, perhaps supported by a tool incorporated into the GP's EMR system that could select these eligible patients.

In conclusion, a more extensive and structured collaboration between health care professionals is desired to facilitate decision making in this heterogeneous patient group, as well as support to simplify the process of selecting patients eligible for a structured medication review, and some on-demand tools for individual consultation.

References:

1. United Nations Department of Economic and Social Affairs Population Division. World population ageing, 2013. New York: *UN*, 2013.
2. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. *Eur J Gen Pract*. 1996;2(2):65–70.
3. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37–43.
4. Payne RA, Avery AJ, Duerden M, Saunders CL, Simpson CR, Abel GA. Prevalence of polypharmacy in a Scottish primary care population. *Eur J Clin Pharmacol*. 2014;70(5):575–581.
5. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. 2007;5(4):345–351.
6. Sinnige J, Braspenning JC, Schellevis FG, Hek K, Stirbu I, Westert GP, Korevaar JC. Inter-practice variation in polypharmacy prevalence amongst older patients in primary care. *Pharmacoepidemiol Drug Saf*. 2016;25(9):1033-1041.
7. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10(4):430–439.
8. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. *Br J Clin Pharmacol*. 2014;77(6):1073–1082.
9. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation. Making it safe and sound. London: *King's Fund*, 2013.
10. Sinnige J, Korevaar JC, Westert GP, Spreeuwenberg P, Schellevis FG, Braspenning JC. Multimorbidity patterns in a primary care population aged 55 years and over. *Fam Pract*. 2015;32(5):505–513.
11. Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC Fam Pract*. 2012;13:56.
12. Luijks HD, Loeffen MJ, Lagro-Janssen AL, van Weel C, Lucassen PL, Schermer TR. GPs' considerations in multimorbidity management: a qualitative study. *Br J Gen Pract.* 2012;62(600):e503-510.
13. Tinetti ME, Bogardus ST, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med.* 2004;351(27):2870–2874.
14. Guthrie B, Payne K, Alderson P, McMurdo ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. *BMJ*. 2012;345:e6341.
15. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. *Implementation Sci*. 2009;4:54.
16. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716–724.
17. Bower P, Macdonald W, Harkness E, Gask L, Kendrick T, Valderas JM, et al. Multimorbidity, service organization and clinical decision making in primary care: a qualitative study. *Fam Pract*. 2011;28(5):579–587.

18. Sinnott C, Hugh SM, Boyce MB, Bradley CP. What to give the patient who has everything? A qualitative study of prescribing for multimorbidity in primary care. *Br J Gen Pract*. 2015;65(632):e184-191.
19. De Jong L, Janssen PGH, Keizer D, Köke AJA, van Bommel M, van Coevorden RS, et al. NHG standard on pain. Utrecht: *NHG nederlands huisartsen genootschap*, 2015. Accessed 20 may 2016. [https://www.nhg.org/standaarden/volledig/nhg-standaard-pijn].
20. Hoes AW, Voors AA, Rutten FH, van Lieshout J, Janssen PGH, Walma EP. NHG standard on heart failure. 2nd rev. [In Ducth]. *Huisarts Wet*. 2010;53(7):368–389.
21. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R, eds. *Analysing qualitative data*. Abingdon: Routledge, 1994:173–194.
22. Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med*. 2011;171(1):75–80.
23. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33(21):2719–2747.
24. Nederlands Huisartsen Genootschap. NHG standard on cardiovascular risk management. 2st rev. [In Ducth]. *Huisarts Wet*. 2012;55(1): 14–28.
25. Task Force on Medicines Partnership, National Collaborative Medicine Management Services Programme. Room for review. A guide to medication review: the agenda for patients, practitioners and managers. London: *Medicines Partnership*, 2002.
26. Moen J, Norrgård S, Antonov K, Nilsson JL, Ring L. GPs' perceptions of multiple-medicine use in older patients. *J Eval Clin Pract.* 2010;16(1):69–75.
27. Smith SM, O'Kelly S, O'Dowd T. GPs' and pharmacists' experiences of managing multimorbidity: a 'Pandora's box'. *Br J Gen Pract*. 2010;60(576):285-294.
28. Luijks H, Lucassen P, van Weel C, Loeffen M, Largo-Janssen A, Schermer T. How GPs value guidelines applied to patients with multimorbidity: a qualitative study. *BMJ Open.* 2015;5(10):e007905.
29. Peabody JW, Luck J, Glassman P, Jain S, Hansen J, Spell M, et al. Measuring the quality of physician practice by using clinical vignettes: a prospective validation study. *Ann Intern Med*. 2004;141(10):771–780.
30. Swennen MH, Rutten FH, Kalkman CJ, van der Graaf Y, Sachs AP, van der Heijden GJ. Do general practitioners follow treatment recommendations from guidelines in their decisions on heart failure management? A cross-sectional study. *BMJ Open.* 2013;3(9):e002982.
31. Veloski J, Tai S, Evans AS, Nash DB. Clinical vignette-based surveys: a tool for assessing physician practice variation. *Am J Med Qual*. 2005;20(3):151–157.
32. Tangliisuran B, Scutt G, Stevenson J, Wright J, Onder G, Petrovic M, et al. Development and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton adverse drug reactions risk (BADRI) model. *Plos ONE*. 2014;9(10):e111254.
33. Fraccaro P, Arguello Casteleiro M, Ainsworth J, Buchan I. Adoption of clinical decision support in multimorbidity: a systematic review. *JMIR Med Inform*. 2015;3(1):e4.
34. Muijrers PE, Grol RP, Sijbrandij J, Janknegt R, Knottnerus JA. Differences in prescribing between GPs: impact of the cooperation with pharmacists and impact of visits from pharmaceutical industry representatives. *Fam Pract*. 2005;22(6):624–630.

35. Florentinus SR, van Hulten R, Kloth ME, Heerdink ER, Griens AM, Leufkens HG, et al. The effect of pharmacotherapy audit meetings on early new drug prescribing by general practitioners. *Ann Pharmacother*. 2007;41(2):319–324.
36. Willeboordse F, Hugtenburg JG, Schellevis FG, Elders PJ. Patient participation in medication reviews is desirable but not evidence-based: a systematic literature review. *Br J Clin Pharmacol*. 2014;78(6):1201–1216.
37. Sinnott C, Mercer SW, Payne RA, Duerden M, Bradley CP, Byrne M. Improving medication management in multimorbidity: development of the MultimorbiditY COllaborative Medication Review And DEcision making (MY COMRADE) intervention using the Behaviour Change Wheel. *Implement Sci*. 2015;10:132.
38. De Grauw WJC, Kaasjager HAH, Bilo HJG, Faber EF, Flikweert S, Gaillard CAJM, et al. Landelijke transmurale afspraak chronische nierschade. [National transmural agreement on chronic renal impairment]. *Huisarts Wet*. 2009;52(12):586–597.
39. Rutten G, De Grauw W, Nijpels G, Houweling B, van de Laar F, Holleman HBF, et al. NHG standard on diabetes mellitus type 2. 3rd rev. *Huisarts Wet.* 2013;56(10):512–525.
40. Smeele IJM, Van Weel C, Van Schayck CP, van der Molen T, Thoonen B, Schermer T, et al. NHG standard on COPD. 2nd rev. [In Ducth]. *Huisarts Wet.* 2007;50(8):362–379.
41. Numans ME, De Wit N, Dirven JAM, Heemstra-Borst CG, Hurenkamp G, Scheele ME, et al. NHG standard on gastric complaints. 3rd rev. *Huisarts Wet.* 2013;56(1):26–35.
42. Van den Bemt P, Tjwa ET, van Oijen MG. Cardiovascular and gastrointestinal safety of NSAIDs. *Ned Tijdschr Geneeskd*. 2014;158:A7311.
43. Belo JN, Bierma-Zeinstra SMA, Raaijmakers AJ, van der Wissel F, Opstelten W. NHG standard on non- traumatic knee problems in adults. 1st rev. *Huisarts Wet*. 2008;51(5):229–240.
44. Janssens HJEM, Lagro HAHM, Van Peet PG, Gorter KJ, van der Pas P, van der Paardt M, et al. NHG standard on arthritis. 1st rev. *Huisarts Wet*. 2009;52(9):439–453.
45. Van Weel-Baumgarten EM, Van Gelderen MG, Grundmeijer HGLM, Licht-Strunk E, van Marwijk HWJ, van Rijswijk HCAM, et al. NHG standard on depression. 2nd rev. *Huisarts Wet*. 2012;55(6):252–259.

Chapter 6

Clinical Medication Reviews in the general practice population: who and why?

J. Sinnige
J.C. Braspenning
F.G. Schellevis
G.P. Westert
J.C. Korevaar

Submitted.

ABSTRACT

Background: Clinical medication reviews (CMR) are increasingly performed in primary care to evaluate patients' prescribed medications. However, there is discussion about the target group for whom a CMR would be (most) useful.

Objective: This study aimed to explore the selection criteria for patients considered as eligible for a CMR according to general practitioners (GP) and pharmacists, and the barriers and facilitators to organize these CMRs.

Methods: Semi-structured interviews with Dutch GPs and pharmacists were held on the performance and organization of CMRs. The questions who they considered eligible for a CMR and why, were discussed based on three selection criteria, namely 1) Dutch guideline on polypharmacy, 2) Dutch Inspectorate of Health Care criterion for a CMR, 3) a Frailty Index. GPs were confronted with three patient lists selected according on these criteria. All interviews were audio-taped, transcribed verbatim and coded thematically.

Results: Five GPs and eight pharmacists were interviewed. They underlined that CMRs should not be restricted to persons of 70 years and older, or solely to those with polypharmacy. The current selection criteria identified an older, frail population who was already frequently monitored, or were institutionalized in a residential home. Important characteristics of patients eligible for a CMR according to the health professionals were: Impaired renal function, signals of non-adherence, regular falls, reduced self-management, lack of medication knowledge, and those using a multi-drug dispensing aid. Mentioned benefits of CMRs were increased medication adherence, increased proactive attitude towards appropriate prescribing, increased patient contact, and the interdisciplinary approach. Difficulties around GP-pharmacist collaboration, and the exchange of patient information hampered the performance of CMRs.

Conclusions: The current selection criteria do not completely correspond with GPs' and pharmacists' perspectives of patient characteristics that are important when considering a CMR. To make CMRs more efficient, changes in the current selection criteria seem needed, as well as improvements in data sharing between health professionals. In addition, GPs and pharmacists together should make strict agreements about the practical organization of CMRs.

INTRODUCTION

Appropriate medication prescribing is essential but challenging in primary care, especially in older multimorbid patients receiving multiple medications (i.e. polypharmacy). Appropriate polypharmacy refers to 'the prescribing of individuals with multiple conditions where medication use has been optimized and where medications are prescribed according to the best evidence'[1]. However, in this patient group prescribing to the best medical evidence is not simple. Because of the heterogeneity of the patients as regards the combination of prevalent diseases and the contextual situation, discrepancies can arise between guideline recommendations and patients' treatment priorities[2]. As a result, there is no apparent, unequivocal, medication management strategy[3]. In addition, these patients are often managed by several health care professionals with the authority to prescribe medications and due to poor inter-professional communication, this may lead to sub-optimal coordination over the medicines[4]. Altogether, this poses a risk for inappropriate medication use, and may lead to adverse drug reactions, falls, or hospital admissions[5].

One possible strategy for the optimization of prescribing is performing a clinical medication review (CMR), which is a critical examination of patients' medications, involving the patient, pharmacist and GP[6]. CMRs have positive effects on the number of medication related problems, patient satisfaction with the medications, and medication adherence[6]. Additionally, when there is a rather intensive GP-pharmacist-patient cooperation, more drug-related problems were identified and solved[6]. However, conclusive positive effects of CMRs on clinical outcomes such as reduced hospital admissions or mortality are still lacking[6]. Furthermore, consensus is lacking on which patients benefit most from CMRs[3, 7].

For the selection of patients for a CMR, criteria are described in available guidelines[8-10]. Most often, these criteria are related to factors like age, number of medications, impaired renal function or history of hospital admissions[9]. The described criteria differ in terms of strictness, which affects the number of patients eligible for a review, and as a consequence, the feasibility for health professionals to select patients for performing CMRs. It turns out to be hard to select patients eligible for a CMR based on the information provided in electronic health record systems[3, 7]. In addition, GPs stated previously that the selection criteria described in the existing guidelines identified patients for whom a CMR may not yet always be needed[3, 7].

When considering the current obligation for Dutch GPs and pharmacists to perform CMRs[10], the question rises how, and for whom, CMRs are currently performed in daily practice. Therefore, the objective of this study is to explore the patient group considered as most eligible for a CMR, by comparing GPs' and pharmacists' perspectives on existing

criteria for identifying patients potentially in need for a CMR. In addition, practical barriers and facilitators for performing CMRs are explored.

METHODS

Semi-structured interviews

To explore opinions and experiences of GPs and pharmacists about three selection criteria for CMRs (1. Dutch guideline on polypharmacy[9]; 2. Dutch Inspectorate of Health Care (IGZ) criterion for a CMR[10]; and 3. Frailty index developed by Drubbel[11]), semi-structured interviews were conducted in 2016. A detailed description of the selection criteria is presented in **Table 1.** The invited GPs were active in a practice that participated in the NIVEL Primary Care Database[12], by which the three sets of CMR selection criteria under study were applied to their own patient population. In **Appendix 6.1** a description of the selection of GPs is given, as well as information related to privacy protection. The community pharmacists were invited through convenience sampling. Baseline characteristics of the participating GPs and pharmacists are presented in **Table 2.** The health professionals were asked about potential eligible patients, the process of structured medication reviews, collaboration between GPs and pharmacists, the existing guidelines on CMRs, and characteristics of patients considered as eligible for a CMR. The first author carried out the interviews, which were all audiotaped with consent of the participants.

Table 1. Methods for identifying older patients potentially in need for a CMR.

Guideline on polypharmacy[9]: *	In this Dutch national guideline it is described that a yearly medication review is required for patients of 65 years and older with polypharmacy (≥ five chronically used medications) and having at least one of the following risk factors; impaired renal function, impaired cognition, increased risk for falls, (signals of) reduced medication adherence, institutionalized, or unplanned hospitalization. We focused on two risk factors that could accurately be determined with routine care data, namely an impaired renal function (eGFR<50 ml/min/1.73m2) or impaired cognition (International Classification of Primary Care (ICPC) codes P20 or P70).
IGZ-criterion[10]: *	The IGZ-criterion is based on the Guideline on polypharmacy, and the Dutch Health Care Inspectorate (IGZ) formulated a more strict criterion to select patients eligible for a medication review, namely 'patients with ≥ 7 chronically used medications and an impaired renal function'.
Drubbel frailty index[11]: *	This frailty index can predict the risk of adverse health outcomes (e.g. emergency department visit, out of hours surgery visit) in the elderly. It is focused on patients' health problems and diseases rather than on patients' prescribed medications and is based on GPs' routine care data. It is based on 36 health deficits which were specified by ICPC codes, and a frailty score was calculated. This score was subdivided into tertiles, and patients in the highest tertile were perceived as 'most frail'. This patient group was selected as potentially eligible for a CMR.

** Originally, several different age categories should be applied in the above mentioned criteria. To compare the criteria, only patients of 75 years and older were selected. This is also the age category formulated in the IGZ-criterion.*

Analysis

To identify the potential target group for a CMR, the three criteria sets were applied to routine care data available in the NIVEL Primary Care database by using STATA version 14.0. STATA was also used to describe the baseline characteristics of the patients that were identified. The semi-structured interviews were transcribed verbatim and coded thematically. A second researcher (JB) checked the thematic codes with the transcribed interviews and in any case of disagreement the two researchers discussed until consensus was reached. Data collection proceeded until saturation was reached, meaning that no new major themes arose from analysis. This was the case after the fifth GP interview and eighth pharmacist interview.

Table 2. Background characteristics of the GPs and pharmacists that were interviewed.

	GP (*N*=5)	Pharmacist (*N*=8)
Gender; male, *n*	3	4
Mean years of work experience [range]	25.5 [21–30]	16.4 [8–34]
Mean days working in the practice [range]	4.3 [3–5]	3.9 [3–5]
Mean number of GPs/pharmacists in the practice [range]	3 [2–5]	2.8 [1–7]
Mean number of cooperating pharmacies/general practices [range]	3.5 [1–7]	9.4 [3–25]
Mean number of pharmaco-therapeutic audit meetings with pharmacists and GPs in a year [range]	5.8 [5–6]	6 [4–10]
Mean number of years that CMRs were performed on a structural basis*	n.a.	3.9 [1–10]

** Only asked to the pharmacists.*

RESULTS

Patient identification based on three selection methods

Nearly all GPs were positive about the suggestion for a tool in the electronic medical record (EMR) system that could select patients for a CMR since there was no functionality in the GPs' EMR system to select patients or to report that a CMR was conducted, besides for the option to make a notation in a free text field. When applying the three selection criteria to the EMR data of patients 75 years and older (61,257 patients from 240 general practices), 11% was considered eligible for a CMR according to the guideline on polypharmacy (6,629 patients), 5% was identified with the IGZ-criterion (3,034 patients), and 3,024 (4.9%) patients were identified with both methods. More specifically, in an average practice of 2168 patients of which 7.2% of the population was ≥75 years in 2013[13], there were 17 and 8 patients eligible for a CMR according to the guideline on polypharmacy or IGZ-criterion, respectively. In **Table 3**, background characteristics of the identified population with the criteria defined in the guideline on polypharmacy and the IGZ-criterion are given. When reflecting on the identified patients, the GPs agreed that these patients were indeed eligible for a CMR. In fact, they mentioned that the

medications of the majority of the selected patients were already reviewed in the past year. However, the identified patients concerned the (very) frail population who were also frequently monitored by the GP and other health professionals, some were institutionalized in a residential home, and part of the patients that were selected with data from 2013 were already passed away at moment of the interview in 2016. The Frailty Index identified far more potentially eligible patients, i.e. 49 patients in an average practice, but not all needed a CMR according to the GPs since they used few medications or used a straightforward combination of medications.

Table 3. Characteristics of the population identified with the guideline on polypharmacy and the IGZ–criterion.

	Guideline on polypharmacy (*N*=6629)	IGZ-criterion (N=3034)
Age; mean (SD)	82.9 (5.1)	83.0 (5.1)
Women, %	64.6	65.9
Number of health deficits; mean (SD) *	6.2 (2.5)	6.6 (2.6)
Heart failure, %	28.7	39.3
Coronary artery disease, %	22.9	26.8
Diabetes Mellitus, %	42.9	50.3
COPD, %	19.1	23.3
Hypertension, %	44.8	46.2
CVA/TIA, %	19.9	19.1
Cancer, %	25.2	26.2
Arthritis/osteoarthrosis, %	39.2	41.5
Urinary problems/incontinence, %	53.1	65.9
Cognitive impairment, %	35.8	12.5
Number of medications; mean (SD)	13.0 (4.4)	14.9 (4.3)
Number of medications chronically used; mean (SD)†	7.7 (2.4)	9.1 (2.1)
Number of chronically used medications in categories, %		
0	0	0
1-4	0	0
5-9	80.7	66.9
10-14	18.0	30.8
≥ 15	1.3	2.3

** According to health deficits used in the Drubbel frailty index (excluding the deficit 'polypharmacy')[11].*
† Chronically used; at least four prescriptions of a medication (ATC3-level) and at least 90 days within the first and last prescription

Eligible target group for a clinical medication review

The IGZ-criterion was an appropriate starting point to select patients according to the health care professionals, but the majority of the participants considered the age limit ≥75 years less suitable, as well as the strict focus on patients with polypharmacy. They indicated that patients younger than 75 years might benefit longer from optimizing their medication regime, and that a CMR can be equally important for those with less than five medications. Other characteristics of an eligible target group for a CMR were: An

impaired cognition, impaired renal function, medication related problems, signals of non-adherence, and signals of problems with managing their own medication use (i.e. self-management problems). The latter two characteristics were a signal to start the use of a multi-drug dispensing aid (MDD). Patients using a MDD were therefore an appropriate group for a CMR. Additional patients for whom extra attention to their medication regime was needed, according to some pharmacists, were non-Dutch speaking elderly and those with regular falls.

Clinical medication reviews and additional activities around medication management

Four out of five GPs indicated that the official pharmacist-led CMRs were conducted annually. These CMRs were nearly always initiated by a pharmacist. The GP, pharmacist, or both health care professionals together, also assessed medication lists of MDD users or of patients recently discharged from hospital. During these medication reconciliations, the patient was not always involved. Patients' medication regime was also evaluated in inhabitants of residential homes, or during the annual extensive GP-consultation for patients involved in integrated care programs of chronic diseases (e.g. diabetes mellitus), or as component of a Frail elderly integrated care program offered by several Dutch health insurance companies. In the Frail elderly program, the GP and patient were involved, and occasionally a specialist in elderly care. Some GPs explicitly stated that they participated in the Frail elderly program to focus on patients who were not selected by the pharmacist for a CMR.

Facilitators and barriers for clinical medication review performance

Selection tools incorporated in the electronic pharmacy system can assist pharmacists in the selection of patients based on the IGZ-criterion or guideline on polypharmacy. To specify this target group even more, some pharmacists added criteria, like a minimal number of potential medication related problems displayed by the electronic tool. However, a limitation was that information, like renal function levels, was not always available or up to date in the system. So, pharmacists could not rely on the tool completely. Furthermore, according to the pharmacists, the initiation of a CMR should not solely be based on the existing selection criteria. Signals of health care providers, caregivers, relatives, or from the requests of patients themselves were also important in the decision to initiate a CMR. Collaboration difficulties between GPs and pharmacists hampered CMR performance. GPs often made official agreements with some -and not all- pharmacies in the area to perform CMRs, and as a consequence not all eligible patients were reviewed. Pharmacists mentioned that the time and effort for performing CMRs outweighed the financial compensation by the health care insurer. Pharmacists also experienced difficulties with organizing appointments for CMRs with GPs. According to the pharmacists this was partly due to the funding model of the GP that for a great part

relies on patient consultations, and because GPs lacked a proactive attitude to perform CMRs. A pharmacist mentioned to be co-located in the general practice, which facilitated inter-professional GP-pharmacist collaboration around pharmacotherapy.

Benefits of clinical medication reviews

Both groups of health care professionals were positive about CMRs. CMRs nearly always resulted in medication adjustments, they noticed increased medication adherence, and because they performed it structurally there were no major changes needed in a patient's medication regime. GPs considered CMRs as an extra trigger to critically assess patients' medications, they were more proactive as regards patients' medication regime, and learned from the interdisciplinary approach. Pharmacists stressed that the performance of CMRs has positioned them more as a health care provider, which they considered positive. They had increased patient contact, and were more informed about patients' social context and wellbeing. They also indicated that CMRs were highly appreciated by the patient. Some pharmacists criticized the missing positive significant clinical patient outcomes.

DISCUSSION

This study showed that the existing criteria for the selection of eligible patients had several disadvantages. GPs and pharmacists mentioned that selection criteria should not merely focus on patients with a high age and number of medications. Furthermore, the initiative for a CMR should be based on signals from health professionals, caregivers or patients themselves rather than on criteria described in guidelines alone. Important patient characteristics to initiate a CMR were; an impaired cognition, impaired renal function, medication related problems, signals of non-adherence, medication self-management problems, regular falls, MDD users, non-Dutch speaking elderly, and those recently discharged from hospital. Issues around GP-pharmacist collaboration and organization hampered the performance of CMRs.

This study underlined two important barriers for successful implementation of CMRs in primary care. The first barrier concerns the current selection criteria. The current selection criteria seem not clear enough. GPs indicated that the criteria identified patients who are already frequently monitored (in a residential home), and pharmacists often added criteria to the selection process to identify a group that is more manageable to review. In line with our results, Geurts et al[7] stated that patients' number of medications and age were not sufficient to define the target group suitable for a CMR and she suggested that risk stratification might be necessary to decide which patients might benefit from a CMR. For patients with an impaired renal function a CMR was

considered important according to the GPs and pharmacists. However, since the renal function values were not always available or up to date, they could not use this information for selecting a target group. An RCT found that patients' renal function did not correlate with a benefit from a CMR, and the same applied for patients' number of diagnoses[14]. To benefit from a CMR, it seemed more effective to select patients with a high number of medications in use, with a high discrepancy between medications prescribed compared to medications actually taken, and with a high Medication Appropriateness Index score[14].
The other barrier concerns collaboration between pharmacists and GPs around the organization of CMRs. GPs in our study perceived that structural agreements with pharmacists about CMRs were lacking. This is contrary to a recent Dutch study that found that 80% of the GPs and pharmacists had made agreements around the organization of CMRs[15]. In line with Kwint et al[16], pharmacists perceived difficulties around the planning and organization of the meetings with GPs about CMRs. Other studies also confirm that difficulties on inter-professional collaboration exist[15, 17]. A major benefit of CMRs for pharmacists was the increase in intensity in patient contact. Previous research showed that while pharmacists agreed on this, GPs disagreed that pharmacists should be involved in monitoring patient's progress, or should have an active role in prescribing medications[18]. Both groups of health professionals did acknowledge that pharmacists should be actively involved in performing CMRs and have a role in supporting GPs in pharmacotherapy[18], but in practice they find it difficult to define each other's role and act accordingly.

This is the first study that investigated whether one could use routine care data for the identification of eligible patients for a CMR, together with views from GPs and pharmacists around important selection criteria and the organization of CMRs. However, the study has a few limitations. The pharmacists' and GPs' views about CMRs might only be partly representative for the general pharmacist and GP population since the GPs turned out to have an above average work experience and the majority of the pharmacists were involved in scientific research, of which some in the field of medication reviews. On the other hand, it considered a group with a lot of experience in prescribing and with clear perceptions about CMRs and the interviews delivered rich information on the subject. Another limitation is that we used data from 2013, while the interviews were held in 2016. As a result, our information of the patients did not always resemble the current status of the patient during the interview in terms of morbidity, medications, frailty, and living situation.

Intensive GP-pharmacist collaboration around CMRs can lead to higher implementation rates of interventions suggested during a CMR[6]. This stresses the importance to solve the communicational and organizational issues around CMRs. Despite of the fact that pharmacies and general practices share data, some information (e.g. renal function

levels) is still not always available or up to date in the pharmacy system. The same applies for certain risk factors that are incorporated in the guideline on polypharmacy (i.e. impaired cognition, hospital admission)[9]. Since both the GPs as well as pharmacists explicitly reported that an impaired renal function, impaired cognition or recent hospital discharge were relevant criteria for a CMR, it is of major importance that GPs continuously share relevant information with the pharmacies visited by their patients -and vice versa. This strongly advocates for an improved exchange of patient information between pharmacy and GP information systems. Further, besides the selection criteria described in the guidelines, GPs and pharmacists seem to highly value more subjective selection criteria, like 'self-management problems' or 'medication side effects', which requires a dialogue with the patient as they are not easily detectable in electronic pharmacy or GP systems. Therefore, one should be alert on signals from the patient themselves, patient's caregivers or relatives, or from different health care providers, like home care assistants. Future research could investigate if these caregivers have the ability to identify patients for whom a CMR has a major benefit. Additionally, one could also explore the possibilities for home care assistants, or community nurses to also share their findings on medication use and patients' health status electronically and structurally with GPs and pharmacists. In this way electronic medical records are enriched with additional information that is relevant when selecting patients for a CMR.
The GPs and pharmacists valued CMRs, but they both fail to implement the reviews on a structural basis. Lack of time and financial support were mentioned reasons, but one of the major issues concerned the difficulty to arrange meetings for CMRs between GPs and pharmacists. It is useful to investigate whether a CMR could be embedded into recurring consultations in the general practice, like the annual consultation for patients participating in integrated care programs for chronic diseases. Collaboration with GPs, as well as data sharing with GPs is likely to improve when a (non-dispensing) pharmacist is located into the general practice. In a limited number of countries this type of pharmacist is already successfully integrated into the general practice, and in the Netherlands this situation is currently under study[19]. Further, to reduce the workload for pharmacists and GPs, and as a result to enhance the feasibility of performing CMRs, a patient questionnaire on actual medication use and drug related problems could replace the face-to-face interview[20].

In conclusion, both the GP as well as pharmacist evaluated CMRs positively as a means to detect medication related problems and improve patients' medication use. Nevertheless, in order to make CMRs feasible in daily practice, the health care professionals should improve data sharing and they should invest in structural inter-professional meetings focused on CMRs. Since the current selection criteria do not completely correspond with GPs' and pharmacists' perspectives of patient characteristics that are regarded important when considering a CMR, changes in the current selection criteria seem also needed by focusing on criteria that are considered important by GPs and pharmacists.

References:

1. Duerden M, Avery AJ, Payne RA. Polypharmacy and medicines optimisation. London: The King's Fund, 2013.
2. Sinnige J, Korevaar JC, Westert GP, Spreeuwenberg P, Schellevis FG, Braspenning JC. Multimorbidity patterns in a primary care population aged 55 years and over. *Fam Pract*. 2015;32(5):505–513.
3. Sinnige J, Korevaar JC, van Lieshout J, Westert GP, Schellevis FG, Braspenning JC. Medication management strategy for older people with polypharmacy in general practice. *Br J Gen Pract*. 2016;66(649):e540-e551.
4. Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med*. 2011;171(1):75–80.
5. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57-65.
6. Geurts MM, Talsma J, Brouwers JR, de Gier JJ. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. *Br J Clin Pharmacol*. 2012;74(1):16-33.
7. Geurts MM, Stewart RE, Brouwers JR, de Graeff PA, de Gier JJ. Implications of a clinical medication review and a pharmaceutical care plan of polypharmacy patients with a cardiovascular disorder. *Int J Clin Pharm*. 2016;38(4):808-815.
8. Clyne W, Blenkinsopp A, Seal R. A Guide to Medication Review. Liverpool: *NHS National Prescribing Centre*, 2008.
9. NHG. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: *Nederlands Huisartsen Genootschap*, 2012.
10. Inspectie voor de Gezondheidszorg. Vastgestelde handhavingsnormen medicatiebeoordelingen. 2015. Accessed 03-02-2017. [https://www.knmp.nl/downloads/vastgestelde-normen-medicatiebeoordeling.pdf].
11. Drubbel I, de Wit NJ, Bleijenberg N, Eijkemans RJ, Schuurmans MJ, Numans ME. Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data. *J Gerontol A Biol Sci Med Sci*. 2013;68(3):301-308.
12. Verheij RA, Koppes LLJ. Verheij RA, Koppes LLJ. Over NIVEL Zorgregistraties eerste lijn. Updated 03-03-2016. Accessed 30-05-2016. [www.nivel.nl/node/4282].
13. CBS Centraal bureau voor de statistiek. Bevolking; geslacht, leeftijd, burgerlijke staat en regio, 1 januari 2013. Updated 29-04-2016. Accessed 05-08-2016. [http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=03759NED&D1=0&D2=113,127-128&D3=0&D4=25&VW=T].
14. Rose O, Mennemann H, John C, Lautenschlager M, Mertens-Keller D, Richling K, et al. Priority Setting and Influential Factors on Acceptance of Pharmaceutical Recommendations in Collaborative Medication Reviews in an Ambulatory Care Setting - Analysis of a Cluster Randomized Controlled Trial (WestGem-Study). *PLoS One*. 2016;11(6):e0156304.
15. Van Dijk L, Bouvy ML, de Bakker D, van der Burgt S, Floor-Schreudering A. Samenwerking tussen huisarts en openbaar apotheker: stand van zaken en mogelijkheden voor de toekomst. Utrecht: *NIVEL*, 2016.

16. Kwint HF, Faber A, Gussekloo J, Bouvy ML. Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: a pragmatic randomized controlled study. *Drugs Aging*. 2011;28(4):305-314.
17. Niquille A, Lattmann C, Bugnon O. Medication reviews led by community pharmacists in Switzerland: a qualitative survey to evaluate barriers and facilitators. *Pharm Pract (Granada)*. 2010;8(1):35-42.
18. Bryant LJ, Coster G, Gamble GD, McCormick RN. General practitioners' and pharmacists' perceptions of the role of community pharmacists in delivering clinical services. *Res Social Adm Pharm*. 2009;5(4):347-362.
19. Hazen AC, Sloeserwij VM, Zwart DL, de Bont AA, Bouvy ML, de Gier JJ, et al. Design of the POINT study: Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team (POINT). *BMC Fam Pract*. 2015;16:76.
20. Willeboordse F, Grundeken LH, van den Eijkel LP, Schellevis FG, Elders PJ, Hugtenburg JG. Information on actual medication use and drug-related problems in older patients: questionnaire or interview? *Int J Clin Pharm*. 2016;38(2):380-387.

Chapter 7

General discussion

GENERAL DISCUSSION

Due to the ageing population, GPs increasingly manage older patients having multiple chronic diseases (multimorbidity). Regular use of several medications is common in this patient group, but appropriate prescribing of combinations of medications is often not evidence-based. This thesis aimed to identify and clarify the challenges and complexity of managing older patients with multimorbidity in general practice, with a special focus on medication management. The studies in this thesis examined the prevalence of multimorbidity patterns in general practice, inter-practice variation as regards the prevalence of polypharmacy, the current medication management strategy of GPs for patients with multimorbidity and polypharmacy, and the potential target group eligible for a clinical medication review (CMR).
In this final chapter the main findings are summarized and discussed. Subsequently, the main methodological issues are described, and the implications for clinical practice and recommendations for future research are presented.

Main findings

Multimorbidity patterns

Although the knowledge about the overall prevalence of multimorbidity is accumulating, insight into the prevalence of specific disease combinations (i.e. morbidity patterns) is limited. Especially this type of information is useful for healthcare providers when managing patients with multimorbidity, since GPs respond to patient's reason for encounter by taking into account all diseases that are prevalent. In *Chapter 2* we found that till 2012, research on the prevalence of multimorbidity patterns for the most part focused on disease pairs. Methodological differences in study setting, data collection method, and the definition of the diseases resulted in considerable variation in prevalence rates of the identified disease pairs. For instance, the prevalence rate of the disease pair depression-hypertension varied from 1.2% to 12.9% between studies. Findings from *Chapter 3* stressed that multimorbidity is not restricted to disease pairs, but is characterized by the presence of complex morbidity patterns, often consisting of various types of chronic diseases. Depending on the disease of interest, there is variation in the complexity of the patterns. More specifically, certain disease triplets are at least five or six times more prevalent in patients with a specific disease of interest, compared to the population without that disease (e.g. cardiac dysrhythmia-osteoporosis or coronary artery disease-COPD in patients with heart failure). On the other hand, some diseases are not specifically bound to a certain pattern, but are equally prevalent in all chronically ill patients (e.g. disease triplets including hypertension or diabetes). Even patients aged 55-69 years with at least one chronic disease had on average three chronic diseases, varying from five diseases for patients with heart failure to two diseases for patients with

migraine. These findings illustrate the heterogeneous nature of this patient group, which leads to a great variety in different treatment options. Furthermore, not only the oldest-old have complex health care needs and require complex management but also those younger than seventy years. Inquiring about patient preferences during the consultation and focusing on what matters to patients seems very relevant for GPs as the disease-specific guidelines can only partly support the treatment decisions.

Variation in medication management of older patients

Because of the limited applicability of current clinical practice guidelines (CPGs), the availability of multiple treatment options, and due to patient and physician perspectives, GPs may vary in the prescribed medications to older patients with complex multimorbidity. Showing this variation, as well as gaining insight into the decision making process as regards medication prescribing can facilitate medication management for these patients. *Chapter 4* shows that of the older population (≥ 55 years) receiving medications, 20% used five of more medications chronically (i.e. polypharmacy). Yet, this prevalence rate varied with a factor 2.4 between general practices (from 12.4% to 30.1%) after accounting for differences in patient population and practice characteristics. An increase in the number of chronic conditions is not directly accompanied by an increase in the number of prescribed medications, since especially the *type* of diseases seems to influence the number of medications prescribed. Discussions with two groups of GPs confirmed that there is no straightforward, apparent medication management strategy for older patients with multimorbidity and polypharmacy (*Chapter 5*). GPs varied in the proposed adjustments of -hypothetical- patients' currently prescribed medications, which is influenced by their assessment of patients' characteristics, social context, life expectancy, and preferences regarding a therapy or medication. Although the GPs had on average 25 years of work experience, they seemed indecisive about the best treatment approach and indicated to value support to facilitate medication management for these patients. Considering the potentially negative consequences of failure in medication management support tools can be valuable, such as structural meetings with other GPs or pharmacists to discuss patients with complex health problems.

Clinical medication reviews for older patients with polypharmacy

Since GPs are receptive for support tools centered around medication management of patients with multimorbidity, we examined clinical medication reviews (CMRs) in more detail. For the selection of eligible patients, criteria are described in guidelines, but these differ in terms of strictness. This affects the number of patients eligible for a review and as a consequence, the feasibility for health care professionals to perform CMRs. In *Chapter 6* we found that the existing selection criteria for patients eligible for CMRs described in the Dutch guideline on polypharmacy[1] or the criteria specified by the Dutch Health Care Inspectorate[2] might be too much focused on frail elderly only. Rather than

patients' age, GPs and pharmacists regarded the following patient characteristics valuable when considering a CMR: an impaired renal function, impaired cognition, signals of medication non-adherence, medication self-management problems, regular falls, patients using a multi-drug dispensing aid, non-Dutch speaking elderly, and those recently discharged from hospital. The GPs as well pharmacists valued CMRs, but they both failed to implement the reviews on a structural basis. Issues around GP-pharmacist collaboration and communication may be solved by improving data sharing between the general practice and pharmacy, and by investing in structural inter-professional meetings focused on CMRs. GPs and pharmacists should put more effort to work as a team when managing older patients with multimorbidity and a complex medication regime.

Interpretation of the findings

Medication management for older patients with multimorbidity turns out to be even more complicated than was expected. A first challenge for GPs concerns the heterogeneity of these patients in terms of the combination of chronic diseases, as well as the patient's unique health context. This sometimes leads to complex medication management, and the question rises how patients with complex medication management can be identified? When these patients are identified, it asks for a management approach involving different care givers, such as the GP and pharmacist. However, issues around collaboration impede adequate decision making around medication prescribing in individual patients. So, how should medication management for these patients be organized? A last challenge relates to the actual treatment approach, for which GPs have to balance between adhering to various disease-specific guidelines and considering patient's personal abilities and preferences.

How to identify patients with a complex medication management?

Findings from *chapter 3* show that older patients with multimorbidity are often characterized by a complex pattern of various types of chronic diseases. Yet, not all multimorbidity patterns lead to a complex medication management. Treatment for patients taking few medications is likely to be (more) straightforward, and the same applies for patients with a 'logical combination' of medications (as mentioned by GPs interviewed -see *chapter 6*). Medications that are (more) commonly combined and described in existing guidelines are prescribed to patients diagnosed with diseases that have a common pathophysiology, like diabetes mellitus and hypertension as risk factors for heart failure[3]. For patients with single diseases and logical disease patterns, case-finding can rely on the recording of the diagnosis -and sometimes a corresponding medication prescription-, according to ICPC- and ATC-codes in GPs' electronic medical records (EMR). One example of effective case-finding applies to the integrated care program for patients with diabetes mellitus type 2; in 2015 over 90% of the so-called 'care

groups' (i.e. a contracting entity of various health professionals that cover all primary care needed by patients with these chronic diseases) identified their total population of patients diagnosed with diabetes mellitus type 2 (DM2) by using the ICPC-code T90[4-6]. However, for patients with a comprehensive set of discordant diseases[7], medication management is far more complicated, and case-finding could not easily be based on an a-priori defined set of ICPC- and ATC-codes, as we showed in *chapter* 6. Nevertheless, when considering a tool to identify patients with complex medication management, a first step could be to exclude the patients with single diseases and those with logical disease patterns. Future research could further investigate (combinations of) factors or patient characteristics that could identify patients with complex care needs, like diagnoses of diseases affecting different body systems, the number of GP consultations in the last year, hospital admission in the last year, or perhaps certain demographic characteristics (socioeconomic status, residential area) that turned out to be reasonable predictors for care burden in general practice[8-10].

Another option to identify patients with a complex medication regime is to make use of an already scheduled consultation at the practice. More specifically, a component of the care provided by the described integrated care programs for chronic diseases is an annual extensive check-up. This check-up can also be used to screen patients on medication related problems, which can indicate complex medication management. Since nearly all patients with DM2 are participating in a disease program[4], and diabetes turned out to be a disease with a comprehensive set of co-occurring diseases (*Chapter 3*), the annual diabetes check-up at the practice seems a promising opportunity for identifying patients with a complex medication regime. An option is to ask patients to complete a short questionnaire about their medication use and potential medication related problems when they are invited for the annual diabetes check-up. Research has shown that questionnaires are able to identify medication related problems, although an actual patient interview provided more information compared to a questionnaire[11-13]. When implemented during annual check-ups for several chronic diseases, it can give the GP an indication of the population with difficulties around the medication regime, and it can reach a major part of the GP's patient population structurally. Besides, this approach fits the pharmacists' and GPs' request to rely more on signals from the patients themselves, rather than on selecting patients based on a predefined set of criteria (i.e. age limit , minimum number of medications, impaired renal function) as described in current guidelines (*Chapter* 6). An important restriction is that such a questionnaire should also be suitable for persons with low(er) literacy skills, which is more often the case for patients who are older, have multimorbidity, or have functional limitations[14]. Future research could elaborate this idea, explore the feasibility for GPs to focus more extensively on patients' medication regime during an annual check-up, could explore whether such a questionnaire is suitable in this patient group, and explore the costs and

benefits for the general practice when GPs, in such a way, focus more proactively on older patients' medication regime.

Organization of care for patients with complex medication management

To provide appropriate treatment for patients with complex medication management, the organization of care should be clear. This is challenged by the fact that management of these patients usually means that several health care professionals are involved[15]; the GP, and (several) medical specialist(s) who are responsible for the treatment. The patient is also often seen by a general practice nurse, and the pharmacist takes care of the patient's medications. Caregivers from the patient's neighborhood who may be involved in patient's management are the district nurse, informal care givers, home care givers or a social care team. So, to have a complete overview of patient's health care needs and social context, information is needed from all these parties. To whom should this information be provided? In several papers and policy documents it is stressed that patients with multimorbidity should have a principal care coordinator[16-19]. Because of the GP's role as gatekeeper, he seems to be in the appropriate position to fulfill this function[20]. Yet, one could also think of assigning a practice nurse for chronic conditions as the coordinator, as she is most often the health care provider seeing patients with one or more chronic conditions receiving integrated care. To date, most practice nurses are well known with the care for patients with diabetes mellitus, and they are increasingly involved in the care for patients with COPD, asthma, cardiovascular diseases, and sometimes even the care for (frail) elderly. However, the GP still is the main care provider, and only he has the authority to adjust the patient's medication regime when needed. The GP is experienced in providing general medicine, usually has a long-established relationship with the (older) patient, and is well-informed about the social context and abilities of the patient. Because of these aspects, the GP seems to be more suitable as a care coordinator than a pharmacist, who is the designated health care professional to maintain an appropriate medication regime, or a specialist in elderly care medicine, who is often only involved at moment when the patient becomes frail, and thus lacks the long lasting relationship and the background information of the patient. In a patient's individual care plan, clear agreements about the designated care coordinator should be made.

A clear organization of care does also mean excellent collaboration and cooperation between the various health care professionals involved. This thesis indicated some of the perceived difficulties when several health care professionals are involved in a patient's management (*Chapter 5* and *Chapter 6*). Other studies also showed that there are difficulties around inter-professional collaboration, care coordination and task distribution[21-25]. For instance, eight percent of chronically ill adults in the Netherlands mentioned that they received conflicting information from their clinicians in the last two

years[21], and GPs and pharmacists differ in their perception who is -and should be-, responsible for the monitoring of patients' medications[22]. So, for the management of patients with a complex medication regime, each of the professionals involved should know his specific role in management and together, they should provide integrated care. This could for instance mean that for older patients with complex multimorbidity GPs, pharmacists and medical specialists work in multidisciplinary care teams in which patient consultations are synchronized, and meetings are regularly organized to maintain the multidisciplinary integrated approach. Even patients, or their representatives, could participate in these meetings to share their experiences. Such a multidisciplinary approach focused on proactive elderly care turned out to be successful on a regional scale in the Netherlands[26]; patients were positive about the proactive approach and healthcare providers perceived improvements in coordination of care, and considered multidisciplinary meetings valuable for the quality of care[26]. This asks for a shared responsibility of the involved health care professionals, and above all the willingness to pursue this multidisciplinary approach. Furthermore, this also requires patients to be more proactive in managing their health. A prerequisite for a shared -and equal- responsibility perhaps also means that certain aspects related to funding should be improved. For instance around the organization of clinical medication reviews (CMR), since lack of sufficient funds was an often heard barrier for implementation according to pharmacists *(Chapter 6*). Appropriate funding, in relation to the time needed to perform a CMR and the time that can't be spent on regular consultations, could facilitate a structural implementation of CMRs in primary care and as such, could improve a multidisciplinary treatment approach.

As mentioned, a multidisciplinary treatment approach does also mean multidisciplinary meetings in which the several health care professionals -at least GPs and pharmacists- can exchange views around pharmacotherapy and medication management. In *chapter 5* we found that GPs would highly appreciate meetings in which they could discuss patients with a complex medication regime. Since medication management for patients with complex multimorbidity often is not completely evidence-based, a common view about a certain pharmaceutical treatment at least could support GPs to follow a consensus-based approach. Besides for the involvement of pharmacists and GPs, perhaps also the patient could attend multidisciplinary meetings, to provide information about his lifestyle, context, social situation, values or preferences. Such information, besides clinical details, could guide the discussion on what kind of medication management would be appropriate[27]. Further, it would lead to patients being more informed and empowered, provide them with an opportunity to ask questions, and would improve communication between the patient and the health care team[28].
A possibly suitable existing meeting to exchange views is the pharmacotherapy audit meeting (in Dutch: Farmacotherapie Overleg (FTO))[29]. In these meetings, GPs and pharmacists discuss medication related topics to gain new and shared insights. The

importance of these FTO-meetings is reflected by the fact that nearly all GPs and pharmacists participate in a FTO-group, and that over 40% of the groups have the highest level of functioning, which is a measure of the quality of these meetings[30]. There is material available to discuss during a FTO-meeting, this concerns for instance topics around diseases, medication transfer, medication reviews, polypharmacy, or medication safety in frail elderly[29]. Some of these topics are likely to be highly valuable for health care professionals to gain insight into the medication management of other professionals. However, a certain topic is most likely on the agenda once or twice a year. In order to structurally imbed a discussion around the pharmacotherapy of patients with a complex medication regime, it seems more valuable that a discussion about a difficult patient case is scheduled for each FTO-meeting.

A multidisciplinary approach is hindered by issues around arranging meetings with all relevant care providers, and perhaps also with the patient (*Chapter 6*). Nevertheless, this could also be reached by structurally gathering the required expertise to one location. More specifically, in several countries a non-dispensing pharmacist is introduced into the general practice, and this is currently investigated in the Netherlands[31-35]. The introduction of the pharmacist in general practice has led to an enhanced ongoing relationship with patients and turned out to make the medication processes run more efficiently. It would enhance knowledge about pharmacology and pharmacotherapy in the practice, and it would enable successful collaboration between the GP and pharmacist as they both have access to important information in patients' medical records, they will share the same vision when working together, which can result in unambiguous pharmaceutical care[36-38]. Future research should especially focus on investigating and solving potential barriers from the GP's perspective, as he does not always thinks pharmacists should have a bigger role as health care providers in primary care[22, 36].

For optimal collaboration and coordination of care, involving several health care professionals, attention should be paid to practical issues as regards patient information sharing, and adequate recording into the various electronic medical record systems (EMR). A patient's individual care plan should be accessible for all health care professionals involved, as well as for the patient himself. For instance, pharmacists and GPs both need the most up to date information about patients' medication history, contra-indications, medication side effects, and biomedical parameters. This information should be exchanged between the various health care providers. To date, the most up to date information is not always available for health care providers, often due to the fact that it is not automatically exchanged between the various systems (*Chapter 6*)[39]. Attention for adequate data sharing and information technology is also perceived a core vision of the Royal Dutch Pharmacists Association (in Dutch: KNMP), the National Dutch General Practitioners Association (in Dutch: LHV) and the Dutch College of General

Practitioners (in Dutch: NHG)[20, 40]. Fortunately, there is a tendency of sharing medical information through electronic tools, and recording systems. Relevant Dutch examples are the 'Landelijk Schakelpunt'[41] and the 'Informatie standaard medicatieproces'[42]. Components of the care for patients with a complex medication regime, like the outcomes of a clinical medication review and the accompanying action points, could also be incorporated into the pharmacist's and GP's EMR system[43]. Again, to accomplish successful information sharing, important prerequisites for the health care professionals --and also for the patient- are a proactive attitude and the willingness to share patient data. In addition, sharing of medical information is -of course-, only possible with explicit consent of patients.

Treatment of patients with complex medication management

When patients with a complex medication regime are identified, appropriate management is necessary. However, this is not easy. To a great extent prescribing of medications relies on the GP's approach because patients with multimorbidity often visit their GP and GPs turn out to be reluctant in consulting a pharmacist or medical specialist when facing a difficult medication regime, as mentioned in *chapter* 5[9, 15]. GPs seem to adhere to the clinical practice guidelines (CPG) when possible, but also (highly) rely on their own previous experience and preferences for a therapy. For decades, GPs are encouraged and educated to adhere to the rapidly increasing collection of CPGs[44], but to date adhering strictly to the disease-specific guidelines is inappropriate when managing patients with multiple diseases with a complex medication regime. This resembles the findings that guidelines do not fit when providing appropriate care to patients during the final stages of life[45]. For this patient group, there is a movement that guidelines should be directed not only at 'action' but also at 'inaction (alternative action)', that shared-decision making is one of the most important basic principles for ensuring appropriate care, and that a multidisciplinary consultative team should be in place that can assist with complex treatment decisions[45]. What should treatment look like for patients with a complex medication management?

Most importantly, management should be highly tailored to the person, and focused on maintaining or improving patient's abilities, and patient's capacity to cope and participate in social activities, in line with the concept of positive health defined by Huber et al[46]. Asking the patient 'what he wants' and 'what is bothering him most' can help to prioritize management to the aspects that will have the highest impact on patients[16, 18, 47]. To elucidate what the patient wants and what he needs to manage his life independently to the very best of his abilities, clear communication is essential. More specifically, it means clear communication from the GP towards the patient, but also from the patient towards the GP. The patient should be adequately informed by the GP about the expected benefits and harms of different medications and treatment options, by also taking into account the patient's level of health literacy[48, 49]. On the other hand, the patient

should have the opportunity, but also take the opportunity and responsibility, to share his concerns about current treatment. For instance about (potential) medication side effects, the complexity of the medication regime, or about non-adherence. This seems a challenge, since patients nowadays still find it hard to express their concerns openly or spontaneously[50, 51]. To create an environment where both parties can actively discuss their concerns and preferences about current treatment, GPs and patients might profit from training or support. For patients, one could think of a patient information leaflet describing patient's 'rights' during a consultation with the GP, or with possible 'example questions' to ask to the GP. An individualized care plan can be used to report the agreed management approach with patient's treatment priorities and abilities. It is necessary to evaluate this plan frequently because of the changes in conditions of life (due to treatment), changing treatment priorities, and to pay attention to possible future problems. Generally, such kind of approach is visualized by the Ariadne principles, see **Figure 1**[18].

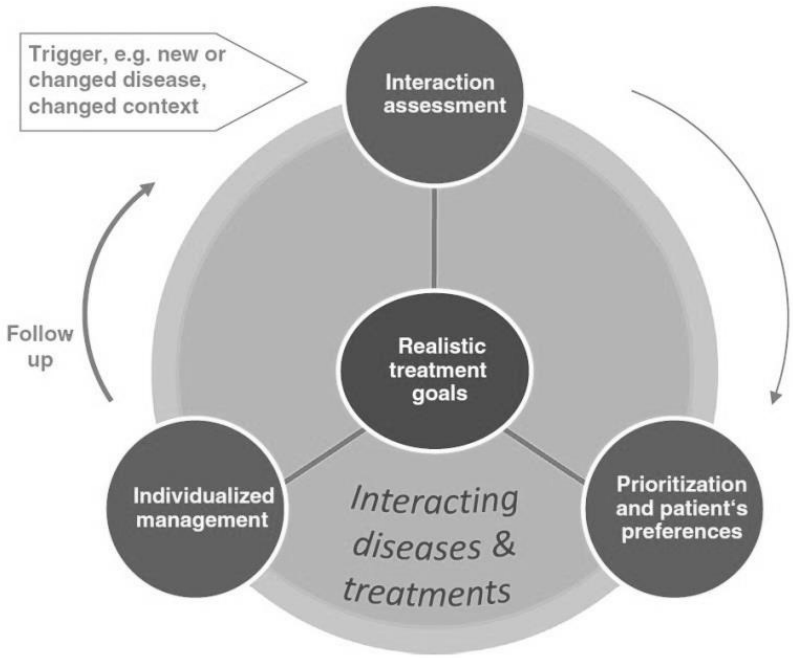


Figure 1. Schematic overview of the management approach based on the Ariadne principles (Muth et al, 2014)[18]

Two promising treatment programs for older patients with a complex medication regime are a clinical medication review, and the integrated care program for frail elderly. Clinical medication reviews have proven to decrease the number of medication related problems and improve patient satisfaction with the medication regime, which seem valuable goals for a patient[52-54]. Embedding a structural medication review as a component of the medication management approach of GPs (and pharmacists) seems therefore promising. However, detecting (potentially) inappropriate medications is only the first step. It should

also result in appropriate action (e.g. adjusting medications, stopping medications, maintaining the current strategy), and GPs sometimes turn out to be indecisive about the best approach, as described in *chapter 5*. So, it is necessary to support GPs in their decision-making process, by providing evidence on appropriate medication combinations and the experience of other health professionals when facing a difficult regime, as described earlier. Future research on medication reviews should still focus on examining clinical outcomes, such as decreased hospital admission rates or improved quality of life, and should investigate potential solutions around organizational issues, for instance the issue around the target group who will benefit most from a medication review.

Integrated care programs for (frail) elderly which are currently only offered on regional level can improve the integrated approach of pharmacists and GPs in the management of patients with -most likely- multiple diagnosed chronic diseases and prescribed medications[26, 55-57]. In line with GPs' and pharmacists' preferences, (C*hapter 6*), case-finding for eligible older patients in these programs also relies on signals of the care providers in general practice, and on signals of caregivers from patients' neighbourhood. In addition, attention for appropriate prescribing is a main element of these programs. Hence, nationwide use of such a care program is suggested to facilitate the medication management process. Future research should investigate its feasibility and effectiveness.

Methodological reflections

The studies in this thesis used various research methods and study populations in order to give an answer on the research questions. **Table 1** provides an overview of the study setting and population per study.

Half of the studies described in this thesis make use of data from the NIVEL Primary Care Database (formerly known as LINH). One of the strengths of using this database is that it already exists for more than two decades. It was therefore possible to determine patients' chronic diseases in a period of 10 years. It also enabled us to use information of at least 40,000 patients and 120 general practices. Furthermore, participating general practices receive quality feedback information about their recordings in the electronic health record system. With this, the participating GPs are particularly aware of their recording habits, and anticipate on the feedback results[58]. So, there is continuous attention for recording uniformly and completely, and therefore the NIVEL Primary Care Database most likely provides complete and reliable patient data.

A second major strength of this thesis is that the findings rely on both quantitative as well as qualitative research. With the quantitative studies we provided important information about multimorbidity patterns and medical practice variation. We used this information as a basis for the focus group interviews and the semi-structured interviews with the GPs and pharmacists. The qualitative studies, therefore, actually explored the perspective of the main healthcare professionals in primary care involved in the (medication) management of patients with multimorbidity. By applying these mixed methods, this

thesis provided suggestions for improvements in the care for patients with multimorbidity.

Table 1. Overview of the examined study population per chapter.

	Systematic review (Chapter 2)	Multimorbidity patterns (Chapter 3)	Variation in polypharmacy (Chapter 4)	Medication management strategy (Chapter 5)	Medication review (Chapter 6)
Setting	General population and general practice	General practice	General practice	General practice	General practice
Type of study population	Patient data from surveys, GPs' EMR	Patient data from GPs' EMR	Patient data from GPs' EMR	GPs discussing hypothetical patients	GPs and pharmacists discussing patients in general
Age patients	At least half of the population in each included study ≥55 years	≥55 years	≥55 years	Hypothetical patients from 68-84 years	≥75 years
Age GPs/pharmacists	n.a.	n.a.	n.a.	Mean age 56yrs	n.a.*
Minimum number of diseases criterion	2	1	0	2	2
Minimum number of medications criterion	0	0	1	5	5
≥1 chronic disease	n.a.	100%	84.6%	n.a.	n.a.
≥1 chronic medication	n.a.	n.a.	81.6%	n.a.	n.a.

** GPs and pharmacists with on average 22 and 16 years of work experience, respectively*

There are some points of deliberation of the work described in this thesis that need to be acknowledged too. One can for instance debate about the chosen disease list in this thesis, because it is known that the number of chosen diseases under study influence the prevalence rate of multimorbidity[59]. To date, this debate is still ongoing and present on the research agenda[60]. From the research perspective, it is wise to have a uniform definition of multimorbidity with the diseases comprising this definition. On the other hand, it still remains complex to manage patients with multimorbidity, regardless of how multimorbidity is defined.

The findings from the two qualitative studies rely on a subgroup of GPs and pharmacists. The GPs in the focus groups were all active as a GP-trainer, which means that they have sufficient work experience and the correct competences, to guide GP residents in their

education. Moreover, it considered a group of GPs interviewed during one of their training days and as such, this group might be extra motivated to provide care according to the guidelines or are perhaps highly alert on a specific topic discussed at the training day. Some pharmacists interviewed about the clinical medication reviews were engaged in research or the development of the guideline criteria for the execution of CMRs. In the two qualitative studies input from less experienced GPs and of pharmacists less involved in research is lacking. In addition, the view of the patients themselves about medication management is missing. This could have enriched the findings in the way that they could have told us about their priorities in medication management.

Implications for research and practice

Based on the studies presented in this thesis, some important points of action can be defined for future research and for health care professionals involved in (medication) management of patients with multimorbidity.

Research implications

Research focused on the concept and outcomes of multimorbidity has received increasing attention over the last decades[61], but comparisons between multimorbidity studies -for instance about the occurrence of multimorbidity- is still hampered by the lack of a uniform definition of multimorbidity. Researchers in the field of multimorbidity should therefore carefully consider (and describe) the number of included diseases, the type of included diseases, and the study setting. Moreover, it may be important to develop a disease list with uniformly defined diseases. When considering the study setting, the general practice setting might be ideal, at least in countries with a strong primary care system. This because there is usually routine care data available, which enables an accurate estimation of patients' full range of morbidity, and it enables longitudinal research to determine the order of the diseases that are diagnosed in a patient. When deliberating a management strategy with the patient, the GP could anticipate on the information that certain diseases -or disease patterns-, are likely to develop in (near) future. Longitudinal research could also contribute to a better understanding of the variation in medication management by following patients with an equal case mix of health conditions and background characteristics and to see what kind of decisions GPs make in management. Yet, one should keep in mind that management in this patient group is most often influenced by several health care providers, and not just the GP. Future research on (medication) management of patients with complex multimorbidity therefore can incorporate the decisions made by medical specialists and pharmacists. Tools could facilitate medication management, but currently none included a patient-centered approach or worked on demand[62], components that were regarded as important by the GPs and pharmacists interviewed in this thesis. Future research can

especially focus on (electronic) tools that can work on demand, to avoid that specific alerts are ignored, and to focus on a target group most in need of additional support. One of such tools could be the annually medication review. However, in its current format it does not focus on the most appropriate target group and difficulties hamper structural implementation. So, future research still should investigate ways to implement this activity efficiently and to perform it effectively.

Practice implications

This thesis showed that medication management for older patients with a complex medication regime asks for a multidisciplinary team managing the patient. It is suggested to at least involve the GP and pharmacist, the practice nurse to support the GP, and to involve a medical specialist for older frail patients. This requires the health care professionals to have the competences and skills to adequately collaborate and communicate to each other and towards the patient. Therefore, training to develop and strengthen these skills during medical education seems necessary, as well as frequently recurring post academic training. Training could also focus on a patient-centered approach to identify patients' needs and preferences and to incorporate these into a feasible treatment plan. For the next generation GPs and pharmacists it should be everyday practice to collaborate intensively with each other when managing patients with complex multimorbidity. Post academic training topics around polypharmacy, medication transfer and medication safety that include GPs as well as pharmacists can stimulate the discussion and exchange ideas and views on a structural basis. Possibilities to facilitate (medication) management in general practice for patients with multimorbidity are to synchronize the appointments of one patient as much as possible so that GPs have the time to focus on what matters to the patient, and in order to reduce the consultation burden for the patient. Furthermore, health care professionals could focus on optimizing the exchange of medical information of patients, to avoid an unnecessary repetition of questions and tests by the various health care providers involved. Besides, it enables all health care providers to have the most up to date patient information which could prevent some of the medication related problems. To facilitate management of patients with a complex medication regime, it also asks for a (policy) system that is more focused on integrated patient-centered care, offering generic care programs with a proactive focus on the care of (frail) elderly. Yet, appropriate attention for the medication regime of younger patients with complex care needs should not be forgotten. Because of the tendency that patients should fulfil an active role in their management[46], it is valuable to enhance patient education as regards disease management, e.g. by providing e-health education, or patient versions of guidelines to involve them in the management process.

General conclusion

Current challenges in general practice as regards managing older patients with multimorbidity concern the heterogeneity of the patients and the absence of a clear medication management strategy. The primary health care system can probably be improved by accounting better for the comprehensive disease patterns that affect the vast majority of the elderly. Our findings show that GPs vary as regards prescribing medications to similar patients. Achieving a more shared vision about the best therapeutic treatment for these patients is likely to add to the effectiveness of patient care, and in addition, would strengthen GPs in their decision-making process. A more structured and adequate collaboration between health care professionals who are involved in patient's medication management may offer better patient outcomes. Such a multidisciplinary approach requires structural meetings between health care providers -and patients- to exchange views and experiences about complex medication management. It also asks for adequate data sharing of patient information in the various electronic medical record systems of the care providers who are involved. Paramount is that the management of patients with multimorbidity and a complex medication regime asks for an approach that is tailored to the person, is evaluated on a frequent basis, and accounts for the patient's specific needs and preferences.

References:

1. NHG. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: *Nederlands Huisartsen Genootschap*, 2012.
2. Inspectie voor de Gezondheidszorg. Vastgestelde handhavingsnormen medicatiebeoordelingen. 08-05-2015. Accessed 03-02-2017. [https://www.knmp.nl/downloads/vastgestelde-normen-medicatiebeoordeling.pdf].
3. Lindenfeld J, Albert NM, Bohmer JP, Collins SP, Ezekowitz JA, et al. Executive Summary: HFSA 2010 Comprehensive heart failure practice guideline. *J Card Fail.* 2010;16:475-539.
4. Klomp M, Romeijnders A, de Braal E, Meluepas M. Transparante ketenzorg rapportage 2015 zorggroepen diabetes mellitus, VRM, COPD en astma, op weg naar genuanceerde rapportage van zorg. Utrecht: *Ineen*, 2016.
5. De Bakker DH, Struijs JN, Baan CB, Raams J, de Wildt JE, Vrijhoef HJ, et al. Early results from adoption of bundled payment for diabetes care in the Netherlands show improvement in care coordination. *Health aff (Millwood).* 2012;31(2):426-433.
6. InEen. Handleiding voor Inclusie en exclusie van patieten in ketenzorgprogramma's. 07-07-2016. Accessed 17-02-2017. [http://ineen.nl/wp- content/uploads/2016/07/160707-InEen-Inclusie-en-exclusiecriteria-ketenzorgprogrammas.pdf].
7. Van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet.* 2006;367:550-551.
8. Harrison C, Britt H, Miller G, Henderson J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open.* 2014;4(7):e004694.
9. Hopman P, Heins MJ, Korevaar JC, Rijken M, Schellevis FG. Health care utilization of patients with multiple chronic diseases in the Netherlands: Differences and underlying factors. *Eur J Intern Med.* 2016;35:44-50.
10. Flinterman L, de Hoon S, De Bakker D, Verheij R. Scenario's voor de differentiatie van het inschrijftarief huisartsenzorg op basis van zorgzwaarte. Utrecht: *NIVEL*, 2016.
11. Willeboordse F, Grundeken LH, van den Eijkel LP, Schellevis FG, Elders PJ, Hugtenburg JG. Information on actual medication use and drug-related problems in older patients: questionnaire or interview? *Int J Clin Pharm.* 2016;38(2):380-387.
12. Makowsky MJ, Cave AJ, Simpson SH. Feasibility of a self-administered survey to identify primary care patients at risk of medication-related problems. *J Multidiscip Healthc.* 2014;7:123-127.
13. Langford BJ, Jorgenson D, Kwan D, Papoushek C. Implementation of a self-administered questionnaire to identify patients at risk for medication-related problems in a family health center. *Pharmacotherapy.* 2006;26(2):260-268.
14. Heijmans M, Waverijn G, Rademakers J, van der Vaart R, Rijken M. Functional, communicative and critical health literacy of chronic disease patients and their importance for self-management. *Patient Educ Couns.* 2015;98(1):41-48.
15. Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M, et al. Review: health care utilization and costs of elderly persons with multiple chronic conditions. *Med Care Res Rev.* 2011;68(4):387-420.
16. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. *BMJ.* 2015;350:h176.

17. Farmer C, Fenu E, O'Flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of NICE guidance. *BMJ.* 2016;354:i4843.
18. Muth C, van den Akker M, Blom JW, Mallen CD, Rochon J, Schellevis FG, et al. The Ariadne principles: how to handle multimorbidity in primary care consultations. *BMC Med.* 2014;12:223.
19. American geriatrics society expert panel on the care of older adults with multimorbidity. Guiding principles for the care of older adults with multimorbidity: An approach for clinicians. *J Am Geriatr Soc.* 2012;60:E1-E25.
20. NHG, LHV. Toekomstvisie huisartsenzorg. Modernisering naar menselijke maat; Huisartsenzorg in 2022. Utrecht: NHG en LHV, 2012.
21. Osborn R, Squires D, Doty MM, Sarnak DO, Schneider EC. In New Survey Of Eleven Countries, US Adults Still Struggle With Access To And Affordability Of Health Care. *Health Aff (Millwood).* 2016;35(12):2327-2336.
22. Van Dijk L, Bouvy ML, de Bakker D, van der Burgt S, Floor-Schreudering A. Samenwerking tussen huisarts en openbaar apotheker: stand van zaken en mogelijkheden voor de toekomst. Utrecht: *NIVEL*, 2016.
23. Moore T, Kennedy J, McCarthy S. Exploring the General Practitioner-pharmacist relationship in the community setting in Ireland. *Int J Pharm Pract.* 2014;22(5):327-334.
24. Chen TF, de Almeida Neto AC. Exploring elements of interprofessional collaboration between pharmacists and physicians in medication review. *Pharm World Sci.* 2007;29(6):574-576.
25. Rubio-Valera M, Jove AM, Hughes CM, Guillen-Sola M, Rovira M, Fernandez A. Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study. *BMC Health Serv Res.* 2012;12:188.
26. Bleijenberg N, de Jonge A, Brand MP, O'Flynn C, Schuurmans MJ, de Wit NJ. Implementation of a proactive integrated primary care program for frail older people: from science to evidence-based practice. *Tijdschr Gerontol Geriatr.* 2016;47(6):234-248.
27. Hamilton DW, Heaven B, Thomson RG, Wilson JA, Exley C. Multidisciplinary team decision-making in cancer and the absent patient: a qualitative study. *BMJ Open.* 2016;6(7):e012559.
28. Butow P, Harrison JD, Choy ET, Young JM, Spillane A, Evans A. Health professional and consumer views on involving breast cancer patients in the multidisciplinary discussion of their disease and treatment plan. *Cancer.* 2007;110(9):1937-1944.
29. Instituut voor Verantwoord Medicijngebruik. Ondersteuning FTO. Accessed: 17-02-2017. [http://www.medicijngebruik.nl/fto].
30. Van Dijk L, Barnhoorn H, de Bakker D. Het Farmaco Therapie Overleg in 1999: stand van zaken en effecten op voorschrijven. Utrecht: *NIVEL*, 2001.
31. Dolovich L, Pottie K, Kaczorowski J, Farrell B, Austin Z, Rodriguez C, et al. Integrating family medicine and pharmacy to advance primary care therapeutics. *Clin Pharmacol Ther.* 2008;83(6):913-917.
32. Tan EC, Stewart K, Elliott RA, George J. Pharmacist consultations in general practice clinics: the Pharmacists in Practice Study (PIPS). *Res Social Adm Pharm.* 2014;10(4):623-632.
33. Bradley F, Elvey R, Ashcroft DM, Hassell K, Kendall J, Sibbald B, et al. The challenge of integrating community pharmacists into the primary health care team: a case study of local pharmaceutical services (LPS) pilots and interprofessional collaboration. *J Interprof Care.* 2008;22(4):387-398.
34. Torjesen I. More than 400 pharmacists will be recruited to GP surgeries by next year. *BMJ.* 2015;351:h6167.

35. Hazen AC, Sloeserwij VM, Zwart DL, de Bont AA, Bouvy ML, de Gier JJ, et al. Design of the POINT study: Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team (POINT). *BMC Fam Pract.* 2015;16:76.
36. Hazen AC, Wal AW, Sloeserwij VM, Zwart DL, Gier JJ, Wit NJ, et al. Controversy and consensus on a clinical pharmacist in primary care in the Netherlands. *Int J Clin Pharm.* 2016;38(5):1250-1260.
37. Mannall C, Cuuts C. Developing clinical pharmacists in general practice, the national learning pathway. Manchester: *Centre for Pharmacy Postgraduate Education, University of Manchester*, 2016.
38. Dolovich L. Ontario pharmacists practicing in family health teams and the patient-centered medical home. *Ann Pharmacother.* 2012;46(4):S33-39.
39. Inspectie voor de Gezondheidszorg. Staat van de gezondheidszorg 2011. Informatie-uitwisseling in de zorg. Utrecht: *Inspectie voor de Gezondheidszorg,* 2011.
40. KNMP. Achtergronddocument Toekomstvisie Farmaceutische Patientenzorg 2020. Den Haag: KNMP, 2014.
41. VZVZ Zorgaanbieders voor zorgcommunicatie. Het LSP. Accessed: 17-02-2017. [https://www.vzvz.nl/page/Zorgconsument/Het-LSP].
42. Nictiz, betere gezondheid door betere informatie. Medicatieproces. Accessed: 17-02-2017. . [https://www.nictiz.nl/projecten/medicatieproces].
43. Geurts MM, Stewart RE, Brouwers JR, de Graeff PA, de Gier JJ. Implications of a clinical medication review and a pharmaceutical care plan of polypharmacy patients with a cardiovascular disorder. *Int J Clin Pharm.* 2016;38(4):808-815.
44. Nederlands Huisartsengenootschap. Ontwikkelen van NHG-Standaarden, versie 2.0. Utrecht: *Nederlands Huisartsen Genootschap,* 2015.
45. Stuurgroep Passende zorg in de laatste levensfase: Niet alles wat kan, hoeft. Utrecht: *KNMG*, 2015.
46. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, et al. How should we define health? *BMJ.* 2011;343:d4163.
47. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
48. Sorensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. *BMC Public Health.* 2012;12:80.
49. Heijmans M, Zwikker H, van der Heide I, Rademakers J. NIVEL Kennisvraag 2016: Zorg op maat. Hoe kunnen we de zorg beter laten aansluiten bij mensen met lage gezondheidsvaardigheden? Utrecht: *NIVEL*; 2016.
50. Zimmermann C, Del Piccolo L, Finset A. Cues and concerns by patients in medical consultations: a literature review. *Psychol Bull.* 2007;133(3):438-463.
51. Butalid L, Verhaak PF, van Dulmen S, Bensing JM. Concerns voiced by patients and GPs' responses during psychosocial visits in primary care: a historical cross-sectional study. *BMC Fam Pract.* 2014;15:188.
52. Willeboordse F, Schellevis FG, Chau SH, Hugtenburg JG, Elders PJM. The effectiveness of optimised clinical medication reviews geriatric patients: Opti-Med a cluster randomised controlled trial. *Fam Pract*. 2017. doi: 10.1093/fampra/cmx007.

53. Leendertse AJ, de Koning GH, Goudswaard AN, Belitser SV, Verhoef M, de Gier HJ, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. *J Clin Pharm Ther.* 2013;38(5):379-387.
54. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol.* 2008;65(3):303-316.
55. PreventZorg, Ketenzorg NU, Leidsche Rijn Julius Gezondheidscentra, Cooperatie Huisartsen Utrecht Stad, Saltro. Regionaal plan Integrale, Proactieve Ouderenzorg Regio Utrecht. 2016. Accessed: 17-02-2017. [http://www.beteroud.nl/docs/beteroud/nieuws/programma-samenwerking-kwetsbare-ouderen-versie-1-feb-2016.pdf].
56. De Feijter C. Pilot met DBC Kwetsbare ouderen. *De Eerstelijns.* 2013;5(8):27-29.
57. VGZ. VGZ Beleid 2016, Zorg voor kwetsbare ouderen. 2016. Accessed: 17-02-2017. [https://www.cooperatievgz.nl/zorgaanbieders/zorgsoorten/huisartsenzorg/documents/d0088-201509%20vgzc%20beleid%202016%20zorg%20voor%20kwetsbare%20ouderen_web.pdf].
58. Van der Bij S, Khan N, Ten Veen P, de Bakker DH, Verheij RA. Improving the quality of EHR recording in primary care: a data quality feedback tool. *J Am Med Inform Assoc.* 2017;14(1):81-87.
59. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann Fam Med.* 2012;10(2):142-151.
60. Le Reste JY, Nabbe P, Lingner H, Kasuba Lazic D, Assenova R, Munoz M, et al. What research agenda could be generated from the European General Practice Research Network concept of Multimorbidity in Family Practice? *BMC Fam Pract.* 2015;16:125.
61. International Research Community on Multimorbidity. Publications on multimorbidity. Accessed: 17-02-2017. [http://crmcspl-blog.recherche.usherbrooke.ca/?page_id=248].
62. Fraccaro P, Arguello Casteleiro M, Ainsworth J, Buchan I. Adoption of clinical decision support in multimorbidity: a systematic review. *JMIR medical informatics.* 2015;3(1):e4.

Chapter 8

Summary

Samenvatting

Appendices

SUMMARY

The presence of multiple (chronic) diseases within one person is known as *multimorbidity*. Due to the aging population, general practitioners (GP) increasingly manage older patients with multimorbidity. Around 55-98% of the persons of 60 years and older is diagnosed with multimorbidity, depending on how multimorbidity is defined and measured. Information is lacking about the prevalence of multimorbidity *patterns*, i.e. specific combinations of diseases that are likely to occur. Many patients with multimorbidity are recommended to use multiple different medications, also referred to as *polypharmacy*. Patients with polypharmacy are at increased risk for inappropriate prescribing, that is the use of medications that should be avoided, and doses or frequencies of medications that should not be exceeded. So, attention for appropriate management and medication prescribing is important. However, issues like fragmentation of care and poor inter-professional communication challenge medication management of older patients with multimorbidity. Furthermore, also the disease-centered approach characterizing the current health care system complicates appropriate management. More specifically, prescribing medications according to recommendations in clinical guidelines may result in an excessive amount of medications with the increased risk of drug interactions, poor adherence and adverse effects. In this older patient group other considerations like patients' quality of life, prognosis, and their treatment preferences can become complementary or even superior to medical motives. A logical result of the limitedly applicable guidelines, the multiple treatment options, and the influence of the physician and patient themselves on the treatment is *variation* in medical practice between physicians. For instance, variation in the (number of) prescribed medications to patients with similar background characteristics. A better understanding of the rational part of medication prescribing variation is needed, as well as insight into factors that influence medication management. Tools or support centered around medication management of patients with multimorbidity seem important.

This thesis aimed to identify and clarify the challenges and complexity of managing older patients with multimorbidity in general practice, with a special focus on medication management.

In **Chapter 1**, we gave an introduction of the concept of multimorbidity and we introduced the problem of medication management of older patients with multimorbidity and polypharmacy. The remaining gaps in knowledge on various aspects of (medication) management for patients with multimorbidity have led to the research questions for this thesis, namely:

1. In an international perspective, which disease combinations are most prevalent?
2. What is the multimorbidity rate in patients with common chronic diseases in the Netherlands, and what kind of multimorbidity patterns occur in older patients with

specific chronic diseases?
3. What is the variation between general practices in polypharmacy rates of older patients?
4. What is the GP's medication management strategy for patients with multimorbidity and polypharmacy?
5. What is the target group eligible for a medication review, from the GP's and pharmacist's perspective, and what are practical barriers and facilitators for performing a medication review?

In **Chapter 2**, we examined the various prevalent disease combinations (i.e. disease patterns) in older patients with multimorbidity, as described in available literature. Our search yielded 3,070 potentially eligible articles of which 23 studies met our quality and inclusion criteria. We found that research on the prevalence of multimorbidity patterns for the most part focused on disease pairs, and there were twenty chronic diseases that were often assessed in patients with multimorbidity. Depression, hypertension, and diabetes mellitus were the most commonly clustered diseases. Methodological differences in study setting, data collection method, and the definition of the diseases resulted in considerable variation in prevalence rates of the identified disease pairs (e.g. the prevalence rate of the disease pair depression-hypertension varied from 1.2% to 12.9% between studies). The identified disease patterns could serve as a first priority setting towards the development of multimorbidity guidelines. A likely option is to start with the most frequently occurring disease combinations and to evaluate possible treatment conflicts, in order to adjust existing clinical guidelines, or to develop new guidelines.

In **Chapter 3**, we determined the multimorbidity rate in older patients with common chronic diseases. We also identified multimorbidity patterns for patients with heart failure, diabetes mellitus, migraine or dementia. We used clinical data of over 120,000 older patients (≥55 years) registered in 158 different general practices in the period 2002-2011. Overall, the multimorbidity rate was 86% for patients with at least one chronic disease, but it varied between 70% for patients with migraine to 98% for patients with heart failure. Chapter 3 stressed that multimorbidity is not restricted to disease pairs, but is characterized by the presence of comprehensive disease patterns, often consisting of various types of chronic diseases. Certain disease patterns were at least five or six times more prevalent in patients with the disease of interest, compared to the population without that disease (e.g. cardiac dysrhythmia-osteoporosis in patients with heart failure). On the other hand, some diseases were not specifically bound to a certain pattern, but were equally prevalent in all chronically ill patients (e.g. disease triplets including hypertension or diabetes). The study also found that multimorbidity is highly prevalent among patients 55-70 years (84%). This study stresses the complexity of multimorbidity, especially because of the heterogeneous nature of the patients. It also illustrates that not only the oldest-old have complex health care needs and require

complex management, but also those younger than seventy years. Guideline developers should be aware of this complexity, and GPs should focus on what matters to the patient, rather than on what is the matter in this patient group.

In **Chapter 4**, we determined the inter-practice variation in polypharmacy prevalence of 44,917 older patients from 86 different general practices. Of the patients of 55 years and older receiving medications, 27% used five of more medications chronically (i.e. polypharmacy). Yet, this prevalence rate varied from 12.4% to 30.1% between general practices after accounting for differences in patient and practice characteristics, with an overall mean of 19.8%. Because considerable inter-practice variation in polypharmacy prevalence existed after accounting for differences in patient and practice characteristics, this suggests that there is not always agreement between GPs concerning medication management in this complex patient group. Physician initiatives to achieve a common vision about the best therapeutic treatment will add to the value and effectiveness of patient care.

In **Chapter 5**, we explored GPs' medication management strategies and their perspectives and needs on decision making support to facilitate medication management. In two focus group meetings, 12 GPs discussed their medication management by means of four clinical case vignettes of patients with multimorbidity and polypharmacy. The discussions confirmed that there is no straightforward, apparent medication management for these patients. GPs varied in the proposed adjustments of -hypothetical- patients' currently prescribed medications. This is influenced by GPs' assessment of patients' background characteristics, social context, life expectancy, and GPs´ preferences regarding a therapy or medication. The GPs seemed indecisive about the best treatment approach, they would like to discuss their choices with other health care professionals, and valued medication reviews with patients. A more structured collaboration between health care professionals is desired, as well as support to facilitate the feasibility of medication reviews with eligible patients.

In **Chapter 6**, we focused on clinical medication reviews (CMR) as a tool to reduce inappropriate medication use. We explored the target group for a CMR, by comparing existing selection criteria with GPs' and pharmacists' perspectives. Furthermore, we explored the barriers and facilitators to organize CMRs. Five GPs and eight pharmacists were interviewed. They both valued CMRs as positive. Important characteristics of patients eligible for a CMR were an impaired renal function, signals of non-adherence, regular falls, reduced self-management, lack of medication knowledge, and a multi-drug dispensing aid. CMRs were nearly always initiated by pharmacists and they selected patients by using electronic selection tools incorporated in their pharmacy system. However, patient information (e.g. renal function levels) in the pharmacy system was not always up to date or available. Patients' medication lists were sometimes evaluated

during the yearly GP-consultation for patients participating in integrated care programs for chronic diseases (e.g. diabetes mellitus), and in patients living in residential homes. The current selection criteria were critically considered by GPs and pharmacists. They mentioned that the initiative for a CMR should be based on signals from health care professionals, caregivers or patients themselves rather than on criteria described in guidelines (e.g. certain age limit). GPs and pharmacists experienced difficulties around inter-professional communication, the arrangement of meetings, and issues around the exchange of patient information between the GP and pharmacist. These organizational issues hamper successful performance of CMRs on a structural basis in daily practice.

In **Chapter 7**, we gave an overview of the results, and discussed the interpretation of the overall findings in this thesis. We addressed three areas of discussion, namely (1) how patients with complex medication management can be identified, (2) how management for patients with a complex medication regime can be organized, and (3) important aspects of treatment of patients with complex medication management. We further addressed some methodological reflections, and we discussed the implications from this thesis for research and practice. To conclude, the research described in this thesis found that the primary health care system can probably be improved by accounting better for the comprehensive disease patterns that affect the vast majority of the elderly. Further, achieving a common vision about the best therapeutic treatment for these patients is likely to add to the effectives of patient care, and in addition, would strengthen GPs in their decision-making process. A more structured and adequate collaboration between health care professionals who are involved in patient's medication management may offer better patient outcomes. Such a multidisciplinary approach asks for structural meetings between health care providers -and patients- to exchange views and experiences about complex medication management. It also requires adequate sharing of patient information in the various electronic medical record systems of the care providers who are involved. Paramount is that the management of patients with multimorbidity and a complex medication regime asks for an approach that is tailored to the person, is evaluated on a regular basis, and accounts for the patient's specific needs and preferences.

Samenvatting

SAMENVATTING

Multimorbiditeit wil zeggen dat één persoon meerdere (chronische) aandoeningen tegelijkertijd heeft. De levensverwachting van mensen stijgt nog steeds en onder andere door de vergrijzing van de samenleving behandelt de huisarts steeds vaker oudere patiënten die multimorbiditeit hebben. Ongeveer 55% tot 98% van de 60-plussers heeft multimorbiditeit, afhankelijk van de gekozen meetmethode en definitie van multimorbiditeit. Er is weinig informatie over de omvang van specifieke combinaties van aandoeningen (*ziekteclusters*) die vaak voorkomen bij patiënten met multimorbiditeit. Veel patiënten met multimorbiditeit gebruiken verschillende geneesmiddelen tegelijk, ook wel *polyfarmacie* genoemd, en hebben daardoor een grotere kans op onjuist en onveilig geneesmiddelengebruik. Aandacht voor een juist medicatiebeleid is daarom belangrijk. Toch wordt het medicatiebeleid bij patiënten met multimorbiditeit bemoeilijkt door een gebrekkige afstemming en continuïteit in de zorg en communicatieproblemen tussen zorgverleners. Een ander knelpunt is de ziektegerichte benadering in de organisatie van de gezondheidszorg. Het voorschrijven van geneesmiddelen zoals aanbevolen in ziekte-specifieke richtlijnen en standaarden kan bij deze groep leiden tot (te) veel geneesmiddelen met het risico op geneesmiddeleninteracties, slechte therapietrouw en andere nadelige effecten. Bij deze oudere patiëntengroep kunnen andere zaken -zoals de kwaliteit van leven van de patiënt, de prognose, of behandelvoorkeuren-, belangrijker worden dan medische motieven. Een logisch gevolg van de beperkt toepasbare richtlijnen, de verscheidenheid aan keuzes in behandelopties, en de invloed van de arts en patiënt zelf op de behandeling is *variatie* in medisch handelen tussen artsen. Bijvoorbeeld, variatie in (het aantal) voorgeschreven geneesmiddelen bij patiënten die dezelfde achtergrondkenmerken hebben. Inzicht in deze medische praktijkvariatie is belangrijk, net als inzicht in factoren die het medicatiebeleid beïnvloeden. Daarnaast is het belangrijk om meer te weten over tools en ondersteuning die als doel hebben het medicatiebeleid bij patiënten met multimorbiditeit te vergemakkelijken en eenduidiger te maken.

Het doel van dit proefschrift was de complexiteit in de behandeling van oudere patiënten met multimorbiditeit in de huisartsenpraktijk in kaart te brengen en te verklaren, met een specifieke focus op het geneesmiddelengebruik en medicatiebeleid.

In **Hoofdstuk 1** gaven we een introductie op het onderwerp multimorbiditeit, als ook een introductie op problemen rondom het medicatiebeleid bij oudere patiënten met multimorbiditeit en polyfarmacie. Dit leidde tot de volgende onderzoeksvragen die in dit proefschrift zijn beantwoord:

1. Welke combinaties van aandoeningen komen vaak voor, zoals beschreven in internationale literatuur?
2. Wat is de omvang van multimorbiditeit in Nederland bij patiënten met

veelvoorkomende chronische aandoeningen, en welke ziekteclusters zie je vaak bij patiënten met enkele specifieke chronische aandoeningen?

3. Wat is de variatie in het percentage oudere patiënten met polyfarmacie tussen huisartsenpraktijken?
4. Hoe ziet het medicatiebeleid eruit van de huisarts bij patiënten met multimorbiditeit en polyfarmacie?
5. Wat zijn de ideeën en opvattingen van huisartsen en apothekers ten aanzien van de criteria voor de selectie van patiënten voor een medicatiebeoordeling, en wat zijn mogelijke praktische faciliterende en belemmerende factoren voor de organisatie van medicatiebeoordelingen?

Hoofdstuk 2 betrof een literatuurstudie naar veelvoorkomende ziektecombinaties -ook wel ziekteclusters genoemd-, bij oudere patiënten met multimorbiditeit. Dit leverde 3.070 mogelijk geschikte artikelen op, waarvan uiteindelijk 23 studies voldeden aan onze kwaliteits- en inclusiecriteria. Onderzoek naar de prevalentie van ziekteclusters bij multimorbiditeit was vooral gericht op ziekteparen en twintig chronische aandoeningen bleken vaak onderzocht te worden. De aandoeningen die het vaakst als cluster voorkwamen waren depressie, hypertensie en diabetes mellitus. Door verschillen in de gekozen studiesetting, methode van dataverzameling, en de gebruikte definitie van de chronische aandoeningen varieerden de prevalentiecijfers van de geïdentificeerde ziekteparen (bijv. de prevalentie van de combinatie depressie-hypertensie varieerde van 1,2% tot 12,9% tussen de studies). De gevonden ziekteclusters zouden als uitgangspunt kunnen dienen bij de ontwikkeling van richtlijnen over multimorbiditeit. Men zou kunnen starten met de meest voorkomende ziektecombinaties, met als doel de mogelijke behandelconflicten te beschrijven, waarmee bestaande richtlijnen kunnen worden aangevuld, of nieuwe ontwikkeld kunnen worden.

In **Hoofdstuk 3** bepaalden we de omvang van multimorbiditeit bij oudere patiënten met veelvoorkomende chronische aandoeningen. Ook brachten we ziekteclusters in kaart van patiënten met hartfalen, diabetes mellitus, migraine of dementie. Hiervoor maakten we gebruik van gegevens van meer dan 120.000 oudere patiënten (≥55 jaar) die ingeschreven waren bij 158 verschillende huisartsenpraktijken in de periode 2002-2011. In totaal had 86% van de patiënten -met een chronische aandoening- multimorbiditeit, maar dit verschilde van 70% voor patiënten met migraine, tot 98% voor patiënten met hartfalen. Deze studie benadrukt dat multimorbiditeit meestal niet betekent dat men twee chronische aandoeningen heeft, maar vaker bestaat uit een cluster van verschillende typen aandoeningen. Bepaalde ziekteclusters kwamen vijf of zes keer zo vaak voor bij patiënten met de specifieke index-ziekte, in vergelijking met de populatie zonder de index-ziekte (bijv. hartritmestoornis-osteoporose bij patiënten met hartfalen). Toch waren er ook aandoeningen die niet specifiek waren voor een bepaald ziektecluster, maar voorkwamen bij alle chronisch zieke patiënten, namelijk ziektecombinaties met hypertensie en diabetes

mellitus. Multimorbiditeit kwam ook vaak voor bij patiënten van 55-70 jaar (84%). Dit onderzoek benadrukt de complexiteit van multimorbiditeit, vooral vanwege de heterogeniteit van de patiënten. Het maakt ook duidelijk dat niet alleen de alleroudsten een complexe zorgvraag hebben welke een complexe behandeling vereist, maar dat dit ook geldt voor patiënten jonger dan 70 jaar. Richtlijnontwikkelaars moeten zich bewust zijn van deze complexiteit, en bij deze patiënten zouden huisartsen zich meer moeten focussen op wat de patiënt belangrijk vindt, in plaats van strikt alle diagnoses willen behandelen.

In **Hoofdstuk 4** onderzochten we de inter-praktijkvariatie in de prevalentie van polyfarmacie bij 44.917 oudere patiënten van 86 verschillende huisartsenpraktijken. Van de patiënten van 55 jaar en ouder die geneesmiddelen gebruikten, gebruikte 27% ten minste vijf geneesmiddelen chronisch (polyfarmacie). De spreiding in het percentage oudere patiënten met polyfarmacie tussen praktijken liep van 12,4% tot 30,1%, nadat gecorrigeerd was voor verschillen in patiënt- en praktijkkenmerken. Gemiddeld had 19,8% van de patiënten polyfarmacie. Omdat de verschillen in het percentage oudere patiënten met polyfarmacie bleven bestaan, nadat er rekening was gehouden met verschillen in patiënt- en praktijkkenmerken, lijkt het erop dat de behandelstijl tussen huisartsen verschilt en er tussen huisartsen onvoldoende overeenstemming is in het medicatiebeleid bij deze complexe patiëntengroep. Initiatieven die leiden tot een gezamenlijke praktijkstijl van artsen over de beste medicamenteuze behandeling zullen bijdragen aan de waarde en effectiviteit van patiëntenzorg.

In **Hoofdstuk 5** brachten we het medicatiebeleid van huisartsen in kaart bij patiënten met multimorbiditeit en polyfarmacie. Ook gingen we na bij huisartsen wat hun opvattingen waren over en hun behoeften aan beslissingsondersteuning om het medicatiebeleid te vergemakkelijken. In twee focusgroepen discussieerden twaalf huisartsen over hun behandelstrategie aan de hand van vier klinische case vignetten van patiënten met multimorbiditeit en polyfarmacie. De gesprekken bevestigden dat er geen eenduidig medicatiebeleid is bij de huisartsen. Huisartsen varieerden in het medicatiebeleid dat zij voorstelden bij deze (hypothetische) patiënten. Dit werd beïnvloed door de afwegingen die zij maakten op basis van de patiënt zijn of haar achtergrondkenmerken, sociale context, levensverwachting en de voorkeuren van de arts wat betreft een behandeling of geneesmiddel. De huisartsen leken niet zeker over de beste behandeling, ze wilden hun keuzes in de behandeling graag bespreken met andere zorgverleners en waardeerden medicatiebeoordelingen met patiënten. Een meer gestructureerde samenwerking tussen zorgprofessionals is daarom gewenst, net als ondersteuning bij de uitvoering van medicatiebeoordelingen bij de juiste doelgroep.

In **Hoofdstuk 6** richtten we ons op medicatiebeoordelingen als een middel om onjuist geneesmiddelengebruik te verminderen. We focusten ons op de mogelijke doelgroep

voor een medicatiebeoordeling door selectiecriteria beschreven in richtlijnen te vergelijken met de visie van huisartsen en apothekers. Daarnaast brachten we in kaart welke knelpunten en faciliterende factoren er zijn bij de organisatie van medicatiebeoordelingen. Vijf huisartsen en acht apothekers werden geïnterviewd en zij bleken allen positief over gezamenlijke medicatiebeoordelingen. Volgens de huisartsen en apothekers waren de volgende kenmerken belangrijke factoren om een medicatiebeoordeling te starten: Een verminderde nierfunctie, signalen van therapieontrouw, geschiedenis van vallen, problemen met zelfmanagement, weinig kennis van de geneesmiddelen, en patiënten die gebruik maken van een medicijnrol. Het initiatief voor een medicatiebeoordeling lag bijna altijd bij de apotheker, die voor de selectie van patiënten vaak gebruik maakte van een tool welke in hun apothekerssysteem ingebouwd is. Echter, bepaalde informatie van de patiënt, zoals nierfunctiewaarden, was niet altijd actueel of aanwezig in het systeem van de apotheek. Het medicatieoverzicht van patiënten die deelnamen aan ketenzorgprogramma's voor chronisch zieken (bijv. voor diabetes mellitus) werd soms geëvalueerd tijdens de jaarcontrole bij de huisarts, en het werd geregeld beoordeeld bij inwoners van verzorgingstehuizen. De huisartsen en apothekers waren kritisch over de huidige selectiecriteria beschreven in de richtlijnen. Het initiatief voor een medicatiebeoordeling zou volgens hen veel meer moeten afhangen van specifieke signalen van zorgverleners, verzorgers of de patiënt zelf in plaats van dat de patiënt voldoet aan bepaalde criteria beschreven in richtlijnen, zoals een leeftijdscriterium. Huisartsen en apothekers benoemden verschillende knelpunten op het gebied van communicatie tussen de twee zorgverleners, het vastleggen van overleg over medicatiebeoordelingen, en er waren problemen rondom de uitwisseling van patiëntinformatie tussen huisartsen en apothekers. Deze knelpunten bemoeilijken de succesvolle uitvoering van medicatiebeoordeling op een structurele basis in de dagelijkse praktijk.

In **Hoofdstuk 7** gaven we een overzicht van de resultaten en bespraken we de interpretatie van de bevindingen van dit proefschrift. We behandelden drie onderwerpen in de discussie, namelijk (1) hoe patiënten met een complex medicatiebeleid geïdentificeerd kunnen worden, (2) hoe het beleid bij patiënten met een complex medicatieregime georganiseerd zou kunnen worden, en (3) belangrijke aspecten van de behandeling van patiënten met een complex medicatiebeleid. Ook bespraken we methodologische kwesties en de implicaties van dit proefschrift voor onderzoek en praktijk. We concludeerden dat de huisartsenzorg verbeterd kan worden door meer rekening te houden met complexe ziekteclusters waar een groot deel van de ouderen mee te maken heeft. Daarnaast kan een meer gezamenlijke visie over de beste medicamenteuze behandeling bij deze patiënten bijdragen aan effectiviteit van de zorg voor de patiënt, en kan het de huisarts helpen in zijn besluitvormingsproces. Een meer gestructureerde en adequate samenwerking tussen zorgverleners die betrokken zijn bij het medicatiebeleid van een patiënt faciliteert het realiseren van betere

patiëntuitkomsten. Zo'n multidisciplinaire benadering vraagt om structurele overlegmomenten tussen de zorgverleners -en patiënten- om ideeën en ervaringen uit te wisselen. Ook vraagt het om optimale uitwisseling van gegevens in de elektronische informatiesystemen van de betrokken zorgverleners. Duidelijk is dat de behandeling van patiënten met multimorbiditeit en een complex medicatieregime vraagt om een benadering die op maat gemaakt is, regelmatig wordt geëvalueerd, en rekening houdt met de specifieke behoeften en voorkeuren van de patiënt.

Appendices

APPENDICES

Appendix 2.1. Electronic literature search strategy for MEDLINE.

Step	Search terms	Studies found
1	multimorbid*[tiab] OR multi-morbid*[tiab] OR multiple morbidit*[tiab] OR multiple diseas*[tiab] OR multiple illness*[tiab] OR multiple diagnos*[tiab] OR multiple chronic diseas*[tiab] OR multiple chronic illness*[tiab] OR multiple chronic diagnos*[tiab] OR multiple chronic condition*[tiab]	2878
2	comorbidity[Mesh] OR comorbid*[ti] OR co morbid*[ti]	58970
3	"chronic disease"[Mesh]	206793
4	#2 AND #3	2969
5	measure[tiab] OR measured[tiab] OR measurement[tiab] OR measurements[tiab] OR measures[tiab] OR index[tiab] OR indexes[tiab] OR indexed[tiab] OR indices[tiab] OR list[tiab] OR listed[tiab] OR lists[tiab] OR classification[tiab] OR classifications[tiab] OR classified[tiab] OR classifies[tiab] OR classify[tiab] OR classifying[tiab] OR instrument[tiab] OR instruments[tiab] OR definition[tiab] OR define[tiab] OR defined[tiab] OR scale[tiab]	3342139
6	#1 AND #5	921
7	#4 AND #5	1230
8	#6 OR #7	2071
9	articles with an abstract available	2064
10	limit #9 to English or Dutch language	1835
11	limit #10 to publications from the year 2000 to current	1602

Appendix 3.1. ICPC-1 codes of the 29 examined chronic diseases.

		ICPC-1 codes
1	Hypertension	K86, K87
2	Diabetes Mellitus	T90
3	Osteoarthritis	L89-L91
4	Coronary artery disease	K74-K76
5	Cancer	A79, B72-B74, D74-D77, L71, N74, R84, R85, S77, T71, U75-U77, W72, X75-X77, Y77, Y78
6	Chronic back or neck disorder	L83, L84, L86
7	COPD	R91, R95
8	Visual disorder	F83, F84, F92-F94
9	Cardiac dysrhythmia	K78-K80
10	Depression (and psychosis)	P73, P76
11	Heart failure	K77
12	Asthma	R96
13	Hearing disorder	H84-H86
14	Osteoporosis	L95
15	Stroke	K90
16	Rheumatoid arthritis	L88
17	Dementia (incl. Alzheimer's disease)	P70
18	Anxiety disorder	P74
19	Migraine	N89
20	Heart valve disorder	K83
21	Neuraesthenia/surmenage/burn-out	P78
22	Chronic alcohol abuse	P15
23	Parkinson's disease	N87
24	Epilepsy	N88
25	Personality disorder	P80
26	Schizophrenia	P72
27	Intellectual disability	P85
28	Congenital cardiovascular anomaly	K73
29	HIV/AIDS	B90

ICPC= International Classification of Primary Care

Appendix 3.2. Detailed information about the analytic techniques of the multiple membership model.

We regarded the diseases of a patient, the patient itself, and the general practices/general practitioners as potential sources of variation for the outcome level. A patient was hierarchical clustered to a specific general practice, and patients were diagnosed with one or multiple diseases, which were not hierarchical distributed to a specific general practice. The focus of this study was to determine the impact of diseases (ranges from 1 to 17 per patient) on the outcome per patient, i.e. multimorbidity (yes/no). This was illustrated in the table below (that showed part of the results also presented in Table 2). The first row of this table (i.e. overall mean) showed the results solely from the perspective of the patient (and thus ignoring the diseases); of the 120,480 patients 62% had multimorbidity (45747 patients with single morbidity and 74733 with multimorbidity). The next 24 rows showed the results from the disease specific perspective; the number of patients with that specific index-disease and the proportion with multimorbidity.

The sum of all numbers in the first column was 273,761 patient-disease cases. This was much more than the actual number of unique patients (120,480). Subsequently, if one calculated the number of patients with single morbidity and multimorbidity per index-disease, the sum was 45747 patients with single morbidity (similar to the number from the patient's perspective) but the multimorbidity number was much higher, namely 228,014 patients. This indicated that patients with multimorbidity were counted several times. This effect was most apparent when one checked the observed proportion of multimorbidity; the 62% of the patient's perspective was outside the range of all disease specific multimorbidity proportions (75%-94%), with an observed average of 85%. To control for the bias due to the fact that patients were counted several times, the effect of the diseases were distributed, proportional to the number of diseases per patient. The multiple membership structure accounts for that; per patient record, each of the 24 diseases allocated a weight. If a disease was present, the weight was one divided by the total number of the diseases per patient. For each patient, the disease weights added up to one. For example, if a patient was diagnosed with five chronic diseases, each of these diseases allocated a weight of 0.20. The disease specific adjusted rate was calculated as the sum of the overall adjusted rate and the disease specific residual estimated from the disease level random effect (the between disease variance). Note that the overall adjusted rate will be more similar to the observed average rate based on the disease specific rates (closer to 85%).

Diseases	**N**	**Observed % Multimorbidity**	**N observed single morbidity**	**N observed multimorbidity**
Overall mean	**120480**	**62.0**	**45747**	**74733**
Heart failure	9520	94.4	537	8983
Heart valve disease	2297	91.9	186	2111
Stroke	7084	90.3	687	6397
Cardiac dysrhythmia	10780	89.6	1124	9656
Coronary artery disease	19145	87.6	2381	16764
Diabetes Mellitus	27007	84.7	4134	22873
COPD	14696	86.7	1950	12746
Visual disorder	13384	88.3	1567	11817
Dementia	3549	85.5	516	3033
Rheumatoid arthritis	3678	85.8	524	3154
Parkinson's disease	1413	84.5	219	1194
Asthma	8774	85.2	1295	7479
Anxiety disorder	3546	84.7	544	3002
Osteoporosis	7981	85.2	1184	6797
Hearing disorder	8076	85.9	1139	6937
Osteoarthritis	20487	83.7	3341	17146
Depression	9758	83.4	1619	8139
Chr. Back or neck disorder	17605	81.6	3234	14371
Alcohol abuse	1528	80.7	295	1233
Cancer	18479	80.5	3606	14873
Epilepsy	1364	81.5	252	1112
Burnout	2288	79.2	475	1813
Hypertension	58658	75.7	14283	44375
Migraine	2664	75.4	655	2009
Total disease-specific N,%	**273761**	**84.7**	**45747**	**228014**

N= number of patients; chr= chronic

Appendix 3.3. Prevalence ratios of disease combinations within the index-disease group compared to the non-index-disease group (patients≥55yrs).

Disease 1: HEART FAILURE * †								
Disease 2 / *Disease 3*	Hypertension	CAD	DM	COPD	Card. dysrhythmia	Osteoarthritis	Cancer	Visual disorder
	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)
Hypertension	-	**2.70** (2.58-2.83)	**1.55** (1.48-1.62)	**2.81** (2.65-2.99)	**3.85** (3.64-4.08)	**1.60** (1.51-1.69)	**1.49** (1.40-1.60)	**1.81** (1.69-1.93)
CAD	**2.70** (2.58-2.83)	-	**3.35** (3.15-3.56)	**5.37** (4.98-5.79)	**6.78** (6.27-7.34)	**3.52** (3.25-3.81)	**3.00** (2.76-3.27)	**3.44** (3.15-3.76)
DM	**1.55** (1.48-1.62)	**3.35** (3.15-3.56)	-	**3.85** (3.56-4.16)	**5.24** (4.83-5.69)	**2.05** (1.89-2.23)	**1.91** (1.74-2.09)	**2.30** (2.11-2.51)
COPD	**2.81** (2.65-2.99)	**5.37** (4.98-5.79)	**3.85** (3.56-4.16)	-	**7.75** (7.04-8.52)	**3.08** (2.78-3.40)	**2.91** (2.64-3.21)	**3.93** (3.55-4.36)
Card. dysrhythmia	**3.85** (3.64-4.08)	**6.78** (6.27-7.34)	**5.24** (4.83-5.69)	**7.75** (7.04-8.52)	-	**4.48** (4.08-4.92)	**4.87** (4.42-5.35)	**5.10** (4.59-5.66)
Osteoarthritis	**1.60** (1.51-1.69)	**3.52** (3.25-3.81)	**2.05** (1.89-2.23)	**3.08** (2.78-3.40)	**4.48** (4.08-4.92)	-	**1.74** (1.57-1.93)	**2.08** (1.88-2.29)
Cancer	**1.49** (1.40-1.60)	**3.00** (2.76-3.27)	**1.91** (1.74-2.09)	**2.91** (2.64-3.21)	**4.87** (4.42-5.35)	**1.74** (1.57-1.93)	-	**1.80** (1.60-2.03)
Visual disorder	**1.81** (1.69-1.93)	**3.44** (3.15-3.76)	**2.30** (2.11-2.51)	**3.93** (3.55-4.36)	**5.10** (4.59-5.66)	**2.08** (1.88-2.29)	**1.80** (1.60-2.03)	-
Back-/neck dis.	**1.17** (1.09-1.27)	**2.54** (2.32-2.79)	**1.53** (1.38-1.69)	**2.30** (2.06-2.57)	**3.44** (3.07-3.86)	**1.32** (1.20-1.47)	**1.32** (1.16-1.50)	**1.73** (1.53-1.97)
Stroke	**2.04** (1.87-2.23)	**4.20** (3.74-4.73)	**2.59** (2.31-2.91)	**4.18** (3.62-4.82)	**5.43** (4.73-6.23)	**3.00** (2.59-3.48)	**2.24** (1.91-2.63)	**2.88** (2.48-3.35)
Hearing disorder	**1.97** (1.80-2.16)	**3.84** (3.43-4.30)	**2.71** (2.39-3.05)	**3.74** (3.26-4.29)	**5.56** (4.86-6.37)	**2.17** (1.90-2.47)	**2.26** (1.96-2.62)	**2.41** (2.10-2.76)
Osteoporosis	**2.14** (1.95-2.34)	**4.59** (4.06-5.18)	**2.85** (2.48-3.27)	**3.66** (3.23-4.16)	**6.58** (5.75-7.54)	**2.08** (1.83-2.37)	**2.06** (1.76-2.40)	**2.60** (2.25-2.99)
Asthma	**1.73** (1.58-1.89)	**4.06** (3.62-4.55)	**2.53** (2.25-2.85)	**2.64** (2.41-2.89)	**5.35** (4.62-6.19)	**1.94** (1.68-2.23)	**2.10** (1.79-2.47)	**2.81** (2.41-3.28)

Disease 1: HEART FAILURE (Continued) * †					
Disease 2 / *Disease 3*	Back/neck dis.	Stroke	Hearing disorder	Osteoporosis	Asthma
	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)
Hypertension	**1.17** (1.09-1.27)	**2.04** (1.87-2.23)	**1.97** (1.80-2.16)	**2.14** (1.95-2.34)	**1.73** (1.58-1.89)
CAD	**2.54** (2.32-2.79)	**4.20** (3.74-4.73)	**3.84** (3.43-4.30)	**4.59** (4.06-5.18)	**4.06** (3.62-4.55)
DM	**1.53** (1.38-1.69)	**2.59** (2.31-2.91)	**2.71** (2.39-3.05)	**2.85** (2.48-3.27)	**2.53** (2.25-2.85)
COPD	**2.30** (2.06-2.57)	**4.18** (3.62-4.82)	**3.74** (3.26-4.29)	**3.66** (3.23-4.16)	**2.64** (2.41-2.89)
Card. dysrhythmia	**3.44** (3.07-3.86)	**5.43** (4.73-6.23)	**5.56** (4.86-6.37)	**6.58** (5.75-7.54)	**5.35** (4.62-6.19)
Osteoarthritis	**1.32** (1.20-1.47)	**3.00** (2.59-3.48)	**2.17** (1.90-2.47)	**2.08** (1.83-2.37)	**1.94** (1.68-2.23)
Cancer	**1.32** (1.16-1.50)	**2.24** (1.91-2.63)	**2.26** (1.96-2.62)	**2.06** (1.76-2.40)	**2.10** (1.79-2.47)
Visual disorder	**1.73** (1.53-1.97)	**2.88** (2.48-3.35)	**2.41** (2.10-2.76)	**2.60** (2.25-2.99)	**2.81** (2.41-3.28)
Back-/neck dis.	-	**2.34** (1.95-2.81)	**1.61** (1.35-1.91)	**1.93** (1.66-2.23)	**1.54** (1.31-1.80)
Stroke	**2.34** (1.95-2.81)	-	**3.58** (2.96-4.33)	**3.51** (2.86-4.29)	**3.83** (3.05-4.82)
Hearing disorder	**1.61** (1.35-1.91)	**3.58** (2.96-4.33)	-	**3.26** (2.70-3.93)	**2.53** (2.04-3.13)
Osteoporosis	**1.93** (1.66-2.23)	**3.51** (2.86-4.29)	**3.26** (2.70-3.93)	-	**2.42** (2.01-2.92)
Asthma	**1.54** (1.31-1.80)	**3.83** (3.05-4.82)	**2.53** (2.04-3.13)	**2.42** (2.01-2.92)	-

Disease 1: MIGRAINE * †							
Disease 2 / *Disease 3*	Hypertension	Back-/neck dis.	Osteoarthritis	Cancer	DM	Depression	CAD
	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)
Hypertension	-	**1.33** (1.17-1.51)	0.90 (0.79-1.03)	**0.78** (0.66-0.93)	**0.55** (0.48-0.64)	**1.24** (1.03-1.50)	**0.71** (0.61-0.83)
Back-/neck dis.	**1.33** (1.17-1.51)	-	**1.57** (1.33-1.86)	1.25 (0.98-1.60)	0.90 (0.71-1.13)	**2.12** (1.68-2.67)	0.96 (0.75-1.23)
Osteoarthritis	0.90 (0.79-1.03)	**1.57** (1.33-1.86)	-	1.09 (0.87-1.38)	**0.71** (0.56-0.90)	**1.68** (1.31-2.15)	0.87 (0.68-1.12)
Cancer	**0.78** (0.66-0.93)	1.25 (0.98-1.60)	1.09 (0.87-1.38)	-	**0.50** (0.32-0.63)	1.28 (0.94-1.76)	**0.57** (0.42-0.78)
DM	**0.55** (0.48-0.64)	0.90 (0.71-1.13)	**0.71** (0.56-0.90)	**0.50** (0.32-0.63)	-	0.74 (0.52-1.05)	**0.50** (0.39-0.65)
Depression	**1.24** (1.03-1.50)	**2.12** (1.68-2.67)	**1.68** (1.31-2.15)	1.28 (0.94-1.76)	0.74 (0.52-1.05)	-	0.93 (0.65-1.34)
CAD	**0.71** (0.61-0.83)	0.96 (0.75-1.23)	0.87 (0.68-1.12)	**0.57** (0.42-0.78)	**0.50** (0.39-0.65)	0.93 (0.65-1.34)	-

Disease 1: DIABETES MELLITUS * †								
Disease 2 / *Disease 3*	**Hypertension**	**CAD**	**Osteoarthritis**	**Cancer**	**Visual disorder**	**Back-/neck dis.**	**COPD**	**Heart Failure**
	Ratio (95% CI)	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**
Hypertension	-	**1.58** (1.52-1.65)	**1.26** (1.21-1.32)	**1.21** (1.15-1.27)	**1.65** (1.57-1.74)	**1.31** (1.25-1.37)	**1.36** (1.29-1.44)	**2.01** (1.89-2.13)
CAD	**1.58** (1.52-1.65)	-	**1.37** (1.27-1.48)	**1.35** (1.25-1.46)	**1.83** (1.69-1.80)	**1.44** (1.33-1.56)	**1.52** (1.40-1.64)	**1.89** (1.76-2.03)
Osteoarthritis	**1.26** (1.21-1.32)	**1.37** (1.27-1.48)	-	1.02 (0.94-1.11)	**1.19** (1.10-1.30)	0.96 (0.89-1.03)	**1.18** (1.07-1.30)	**1.64** (1.49-1.80)
Cancer	**1.21** (1.15-1.27)	**1.35** (1.25-1.46)	1.02 (0.94-1.11)	-	**1.25** (1.14-1.37)	0.98 (0.89-1.08)	1.05 (0.96-1.15)	**1.45** (1.31-1.61)
Visual disorder	**1.65** (1.57-1.74)	**1.83** (1.69-1.80)	**1.19** (1.10-1.30)	**1.25** (1.14-1.37)	-	**1.31** (1.20-1.45)	**1.40** (1.27-1.55)	**2.11** (1.91-2.34)
Back-/neck dis.	**1.31** (1.25-1.37)	**1.44** (1.33-1.56)	0.96 (0.89-1.03)	0.98 (0.89-1.08)	**1.31** (1.20-1.45)	-	**1.11** (1.01-1.23)	**1.78** (1.58-2.01)
COPD	**1.36** (1.29-1.44)	**1.52** (1.40-1.64)	**1.18** (1.07-1.30)	1.05 (0.96-1.15)	**1.40** (1.27-1.55)	**1.11** (1.01-1.23)	-	**1.54** (1.41-1.67)
Heart Failure	**2.01** (1.89-2.13)	**1.89** (1.76-2.03)	**1.64** (1.49-1.80)	**1.45** (1.31-1.61)	**2.11** (1.91-2.34)	**1.78** (1.58-2.01)	**1.54** (1.41-1.67)	-

Disease 1: DEMENTIA * †								
Disease 2 / *Disease 3*	**Hypertension**	**DM**	**Heart Failure**	**CAD**	**Osteoarthritis**	**Cancer**	**Visual disorder**	**Depression**
	Ratio (95% CI)	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**	**Ratio (95% CI)**
Hypertension	-	0.92 (0.83-1.01)	**2.17** (1.93-2.43)	1.09 (0.98-1.22)	1.01 (0.91-1.13)	**0.86** (0.75-0.99)	1.12 (0.98-1.28)	**1.64** (1.42-1.89)
DM	0.92 (0.83-1.01)	-	**2.10** (1.81-2.43)	1.11 (0.96-1.29)	**1.36** (1.17-1.59)	**1.26** (1.06-1.50)	1.19 (1.00-1.42)	**1.88** (1.54-2.29)
Heart Failure	**2.17** (1.93-2.43)	**2.10** (1.81-2.43)	-	**2.08** (1.81-2.40)	**2.37** (2.00-2.83)	**2.16** (1.78-2.63)	**2.59** (2.15-3.13)	**3.88** (3.14-4.79)
CAD	1.09 (0.98-1.22)	1.11 (0.96-1.29)	**2.08** (1.81-2.40)	-	**1.31** (1.10-1.56)	**1.28** (1.06-1.54)	**1.42** (1.18-1.72)	**2.28** (1.86-2.81)
Osteoarthritis	1.01 (0.91-1.13)	**1.36** (1.17-1.59)	**2.37** (2.00-2.83)	**1.31** (1.10-1.56)	-	**1.22** (1.00-1.47)	**1.41** (1.18-1.70)	**1.90** (1.55-2.34)
Cancer	**0.86** (0.75-0.99)	**1.26** (1.06-1.50)	**2.16** (1.78-2.63)	**1.28** (1.06-1.54)	**1.22** (1.00-1.47)	-	**1.38** (1.13-1.70)	**1.97** (1.57-2.47)
Visual disorder	1.12 (0.98-1.28)	1.19 (1.00-1.42)	**2.59** (2.15-3.13)	**1.42** (1.18-1.72)	**1.41** (1.18-1.70)	**1.38** (1.13-1.70)	-	**2.35** (1.85-2.99)
Depression	**1.64** (1.42-1.89)	**1.88** (1.54-2.29)	**3.88** (3.14-4.79)	**2.28** (1.86-2.81)	**1.90** (1.55-2.34)	**1.97** (1.57-2.47)	**2.35** (1.85-2.99)	-
Stroke	**1.96** (1.71-2.24)	**2.53** (2.13-3.02)	**3.54** (2.88-4.34)	**1.93** (1.54-2.43)	**2.42** (1.92-3.07)	**1.99** (1.54-2.57)	**2.04** (1.58-2.63)	**3.28** (2.55-4.20)
Card. dysrhythmia	**1.28** (1.12-1.47)	**1.48** (1.23-1.80)	**2.54** (2.18-2.95)	**1.64** (1.37-1.97)	**1.70** (1.39-2.06)	**1.73** (1.41-2.13)	**2.04** (1.66-2.51)	**2.98** (2.33-3.81)
COPD	**0.82** (0.70-0.96)	0.95 (0.77-1.17)	**1.78** (1.50-2.12)	**1.27** (1.05-1.54)	1.08 (0.85-1.36)	1.11 (0.89-1.38)	**1.31** (1.04-1.66)	1.31 (0.99-1.73)

Disease 1: DEMENTIA (Continued) * †			
Disease 2 / *Disease 3*	**Stroke**	**Card. dysrhythmia**	**COPD**
	Ratio (95% CI)	**Ratio (95% CI)**	**Ratio (95% CI)**
Hypertension	**1.96** (1.71-2.24)	**1.28** (1.12-1.47)	**0.82** (0.70-0.96)
DM	**2.53** (2.13-3.02)	**1.48** (1.23-1.80)	0.95 (0.77-1.17)
Heart Failure	**3.54** (2.88-4.34)	**2.54** (2.18-2.95)	**1.78** (1.50-2.12)
CAD	**1.93** (1.54-2.43)	**1.64** (1.37-1.97)	**1.27** (1.05-1.54)
Osteoarthritis	**2.42** (1.92-3.07)	**1.70** (1.39-2.06)	1.08 (0.85-1.36)
Cancer	**1.99** (1.54-2.57)	**1.73** (1.41-2.13)	1.11 (0.89-1.38)
Visual disorder	**2.04** (1.58-2.63)	**2.04** (1.66-2.51)	**1.31** (1.04-1.66)
Depression	**3.28** (2.55-4.20)	**2.98** (2.33-3.81)	1.31 (0.99-1.73)
Stroke	-	**2.47** (1.92-3.18)	**1.57** (1.16-2.12)
Card. dysrhythmia	**2.47** (1.92-3.18)	-	**1.41** (1.11-1.79)
COPD	**1.57** (1.16-2.12)	**1.41** (1.11-1.79)	-

CAD=coronary artery disease; DM=Diabetes Mellitus; Card.=cardiac; Back-/neck dis=Back or neck disorder

** Ratios and confidence intervals were based on crude prevalence rates*

† Bold numbers: statistically significant ratios (p<0.05), statistically more prevalent in the index-disease group compared to the non-index-disease group

Appendix 5.1. Adams: description of fictionalized case vignette with possible treatment considerations.

Mrs Adams, 71 years old, visits her GP after completing her high-dosage prednisolone treatment. For 10 years, Mrs Adams has been diagnosed with moderate COPD. The GP is her main clinician, because she is considered a patient with stable COPD. In the last 14 months, Mrs Adams experienced three acute exacerbations of COPD, for which short courses of systemic corticosteroids were prescribed (prednisolone 30 mg o.d. for 7 days). During the consultation, Mrs Adams tells the GP that she does not experience severe shortness of breath any more, but she does feel somewhat airless, and, until recently, she has had headaches quite often, she feels tired, and she has a frequent need to urinate. In 2007, Mrs Adams was diagnosed with diabetes mellitus type 2, and at the end of 2012 she suffered a TIA. Moreover, she has high blood pressure and impaired renal function. Mrs Adams and her husband still live together independently at home. For over 40 years, Mrs Adams had been a heavy smoker, but she gave up smoking in 2004, when diagnosed with COPD. Mrs Adams works in a library one afternoon in the week, and walks with her daughter twice a week.

Prescribed medications:	**(laboratory) test results:**	**Visit: (20/05/2014)**	**Visit: (30/07/2014)**	**Current visit: (01/10/2014)**
Metformin 1000 mg t.i.d. Gliclazide 80 mg b.i.d. Acetylsalicylic acid 80 mg o.d. Dipyridamole 200 mg b.i.d. Simvastatin 40 mg o.d. Hydrochlorothiazide 25 mg o.d. Salbutamol 200µg q.i.d., prn. Tiotropium 18µg o.d. Omeprazole 20 mg o.d. Alendronic acid 10 mg o.d.	Blood pressure (mmHg): eGFR (ml/min/1.73m^2): Albumin/Creatinine ratio (mg/mmol): LDL cholesterol (mmol/l): HbA1c (mmol/mol): Fasting blood glucose level (mmol/l): BMI (kg/m^2):	150/91 42 3.6 3.0 52 7.0 30	150/92 42 3.6 3.0 57 7.1 30	149/91 41 3.6 2.8 61 8.1 30

Points of concern: Diabetes control, impaired renal function, blood pressure, dyspnoea

Possible treatment considerations based on separate Dutch CPGs:

•Lower the metformin dosage. In patients with a renal function at 30–50 ml/min, the maximum metformin dose is 500 mg b.i.d.[38].

•Consider starting with insulin. Insulin is considered since the HbA1c target (<58 mmol/mol) was not met, despite the maximum metformin dosage[39].

•Change the dosage of hydrochlorothiazide into 12.5 mg o.d. For hypertension treatment, an ACE inhibitor is preferred in patients with diabetes mellitus type 2 and microalbuminuria (loss of 3.5–35 mg albumin/mmol creatinine in women)[24].

•Start with an ACE inhibitor. Despite the current hydrochlorothiazide dose, the recommended systolic blood pressure level of ≤140 mmHg was not achieved, therefore additional medication is recommended. An ACE inhibitor is preferred in patients with type 2 diabetes mellitus and microalbuminuria (loss of 3.5– 35 mg albumin/mmol creatinine in women)[24]. The recommendation is to stop the hydrochlorothiazide for 2–3 days, and then start with the ACE inhibitor and hydrochlorothiazide.

•Change simvastatin into atorvastatin 20 mg o.d. If the LDL cholesterol target of <2.5 mmol/l is not met with simvastatin, the recommendation is to change to the preferred second step in cholesterol therapy[24].

•A common side effect of dipyridamole is headache. In patients with complaints related to dipyridamole, one can consider giving acetylsalicylic acid alone[24] Clopidogrel is an alternative to prevent myocardial infarction (MI) and stroke; if complaints occur related to the use of acetylsalicylic acid, change acetylsalicylic acid into clopidogrel.

•Consider starting with inhaled corticosteroids. Inhaled corticosteroids are considered for patients with frequent exacerbations[40]. If it is decided not to start with inhaled corticosteroids, stop with omeprazole; the patient finished the 7-day high-dose oral corticosteroids course, and consequently the use of a proton pump inhibitor is no longer indicated for this patient[41].

•Consider consulting a nephrologist. Recommended in patients >65 years with an eGFR between 30 and 45 ml/min/1.73 m2 [38].

Appendix 5.2. Brown: description of fictionalized case vignette with possible treatment considerations.

Mr Brown, 68 years old, was asked to visit his GP, as laboratory tests showed a decline in renal function. At the end of 2012, he suffered an MI and since then he uses several medicines as measures for secondary prevention after MI. In 2009, Mr Brown was diagnosed with osteoarthritis. An NSAID was prescribed for pain management because treatment with paracetamol had insufficient effect, and during treatment with tramadol he experienced nausea. Mr Brown lives alone, and quited smoking at the age of 60. He intended to cycle every day, but is not always able to do this because of pain, especially in the knees. Last August, a diuretic was prescribed because of his high blood pressure, and the GP evaluated Mr Brown's sodium intake and lifestyle. In November, his blood pressure was hardly lowered, and therefore an ACE inhibitor was prescribed.

Prescribed medications:	**(laboratory) test results:**	**Visit: (21/08/2014)**	**Visit: (12/11/2014)**	**Current visit: (15/12/2014)**
Naproxen 250 mg b.i.d. Acetylsalicylic acid 80 mg o.d. Metoprolol 100 mg o.d. Simvastatin 40 mg o.d. Hydrochlorothiazide 12.5 mg o.d. Enalapril 5mg o.d. Omeprazole 20 mg o.d.	Blood pressure (mmHg): eGFR (ml/min/1.73m^2): Albumin/Creatinine ratio (mg/mmol): LDL cholesterol (mmol/l): Fasting blood glucose level (mmol/l):	165/100 52 2.3 3.0 4.8	160/100 50 2.4 3.1 4.7	158/96 42 2.8 3.1 4.8

Points of concern: Blood pressure, cholesterol, use of naproxen, pain

Possible management considerations based on separate Dutch CPGs:

•Stop naproxen. Use of an NSAID, in combination with acetylsalicylic acid, is discouraged due to gastric complications, and because NSAIDs stimulate sodium and water retention, which increases the risk for (or worsens) impaired renal function, high blood pressure, and heart failure. It is further discouraged in patients with an MI[19, 42].

•Start with paracetamol/acetaminophen (with codeine) as an alternative for naproxen, or consider morphine therapy, or corticosteroid injections in the knee. All as possible alternatives for pain treatment[18, 40].

•Increase ACE inhibitor dosage. The recommended systolic blood pressure level of ≤140 mmHg is not achieved with the current dosage of hydrochlorothiazide and enalapril[24].

•Consider changing simvastatin into atorvastatin 20 mg o.d. If the LDL cholesterol target of <2.5 mmol/l is not met with simvastatin, the recommendation is to change to the preferred second step in cholesterol therapy [24].

•Assess possibilities for a knee brace, or knee arthroplasty. In view of the patient's age and physical condition, surgery could be considered as an option[43].

Appendix 5.3. Smith: description of fictionalized case vignette with possible treatment considerations.

Mrs Smith, 84 years old, visits her GP with complaints about dizziness. During the consultation, she further indicates that she has sleeping problems due to shortness of breath and a frequent need to urinate. Mrs Smith was weighed and had gained 4 kg since her last visit. She has had hypertension since 1999, and osteoporosis since 2000. Concerning her osteoporosis treatment, she used alendronic acid for 5 years. In 2002, Mrs Smith was diagnosed with type 2 diabetes mellitus, and in 2008 she was diagnosed with cardiac dysrhythmia, for which she receives anticoagulation medication from an anticoagulation clinic. Since 2014, she has had heart failure with symptoms of fluid retention, and therefore furosemide is prescribed. She lives alone, and generally stays indoors. Mrs Smith's daughter visits her twice a week with groceries, and to give practical household help.

Prescribed medications:	**(laboratory) test results:**	**Visit: (03/10/2014)**	**Current visit: (06/11/2014)**
Calcium/vitamin D 600/400 o.d.	Blood pressure (mmHg):	148/92	149//92
Paracetamol 500 mg t.i.d.	Ventricular rate (bpm):	89	92
Metoprolol 100 mg o.d.	eGFR (ml/min/1.73m^2):	46	42
Lisinopril 5 mg o.d.	Albumin/Creatinine ratio (mg/mmol):	2.4	2.6
Furosemide 40 mg o.d.	LDL cholesterol (mmol/l):	2.5	2.5
Simvastatin 40 mg o.d.	HbA1c (mmol/mol):	58	58
Metformin 500 mg b.i.d.	Fasting blood glucose level (mmol/l):	4.8	
Phenprocoumon from an anticoagulation clinic	Random blood glucose level (mmol/l):		6.3
	Sodium (mmol/l):	138	132
	Potassium (mmol/l):	4.0	3.9
	INR:	2.8	2.5

Points of concern: Dizziness, dyspnoea, oedema/increase in weight, blood pressure

Possible treatment considerations based on separate Dutch CPGs:

- Increase furosemide dosage. Patient's rapid increase in weight, and dyspnoea at night, can indicate fluid retention, possibly insufficiently treated by the current dosage of furosemide; furosemide promotes the loss of excess fluid in patients with heart failure[20]. Monitor serum electrolytes frequently, in view of the increased furosemide dosage and her decreased sodium values.
- Enquire as to type of dizziness. There are several reasons for dizziness, for instance, dizziness due to orthostatic hypotension, or due to a side effect of the medications. Insight into the type (or cause) of dizziness can influence treatment.
- Increase lisinopril dosage to control the blood pressure, and to improve the blood flow[20].
- Consider increasing the metoprolol dosage, but only after treatment for the heart failure exacerbation[20].
- Consider starting with spironolactone if adjusting the furosemide, lisinopril, and metoprolol dosages does not result in reduced fluid retention and dyspnoea[20].

Appendix 5.4. Turner: description of fictionalized case vignette with possible treatment considerations.

Mr Turner, 71 years old, visits the GP with a severe pain attack in his big toe. It is too painful to even touch his toe. During the consultation, Mr Turner points out that he had experienced several attacks of severe pain in his foot; however, up until now, using paracetamol was often an adequate analgesic and, therefore, he had not mentioned it to his GP. This week, paracetamol could not alleviate the pain. A blood test demonstrated an elevated uric acid level, and considering his previous pain attacks Mr Turner was diagnosed with gout. Since 2008, Mr Turner has cardiac dysrhythmia and in 2012 he suffered a TIA. He also has high blood pressure. In 2014, his wife passed away, which resulted in depression. Paroxetine was prescribed, and he has been using paroxetine for 6 months.

Prescribed medications:	**(laboratory) test results:**	**Visit: (07/10/2014)**	**Current visit: (03/11/2014)**
Acenocoumarol from an anticoagulation clinic Paroxetine 20 mg o.d. Metoprolol 50 mg o.d. Hydrochlorothiazide 12.5 mg o.d. Simvastatin 40 mg o.d. Omeprazole 20 mg o.d.	Blood pressure (mmHg): Ventricular rate (bpm): eGFR (ml/min/1.73m^2): Albumin/Creatinine ratio (mg/mmol): LDL cholesterol (mmol/l): Fasting blood glucose level (mmol/l): Uric acid (mmol/l): INR: BMI (kg/m^2):	150/92 92 49 2.6 2.4 4.8 3.1 27	148/91 92 49 2.6 2.4 0.46 3.6 27

Points of concern: (Pain due to) gout attack, blood pressure, depression treatment

Possible treatment considerations based on separate Dutch CPGs:

•Stop omeprazole. It is unknown if the patient has gastric complaints, and the patient does not use an NSAID or a low-dose acetylsalicylic acid (LDASA), and therefore a proton pump inhibitor is not indicated[41].

•Start prednisolone 30 mg o.d. for 5 days. Short-term use of systemic corticosteroids can be effective in treating gout attacks, when NSAIDs are contraindicated[44].

•Add an ACE inhibitor. The recommended systolic blood pressure level of ≤140 mmHg is not achieved with the current dosage of metoprolol. It is recommended to stop the hydrochlorothiazide for 2–3 days, and then start again with the ACE inhibitor and hydrochlorothiazide[24].

•Monitor use of paroxetine. Enquire about effects of treatment and consider stopping or changing the medication if the patient does not perceive any effect. Long-term use of paroxetine is discouraged[45].

Appendix 6.1. Selection of the interviewed GPs and patients and information related to privacy protection.

The selection of GPs to interview preceded in several steps. The selection criteria were applied to data of patients from 240 different general practices. General practices were excluded when more than 60 patients were identified with the IGZ-criterion, and practices were excluded with less than five patients identified when combining all three criteria. GPs from ten general practices were invited by email to participate. These ten practices were chosen based on accessibility of the practice location. Data of practices that agreed to participate was inspected to select a final patient group that was discussed during the interview. We intended to choose distinct patients as regards age, gender, number of medications, type and number of diagnoses and chronic diseases.

NIVEL handles the NIVEL Primary Care Database data in accordance with the Dutch Data Protection Act which ensures that researchers do not have access to identifiable patient information. Therefore, a data manager of the database sent a secured email to the participating GPs with instructions how to select the patients according to the three criteria sets. For this action, we had permission by an internal privacy protection committee. In addition, both the participating GPs as well as the researcher carrying out the interviews signed a document ensuring privacy protection of the discussed patients.

Chapter 9

List of publications

Dankwoord

About the author

RIHS PhD portfolio

LIST OF PUBLICATIONS

Sinnige J, Braspenning J, Schellevis F, Stirbu-Wagner I, Westert G, Korevaar J. The prevalence of disease clusters in older adults with multiple chronic diseases – a systematic literature review. PLoS ONE. 2013; 8(11): e79641. doi:10.1371/journal.pone.0079641.

Sinnige J, Korevaar JC, Westert GP, Spreeuwenberg P, Schellevis FG, Braspenning JC. Multimorbidity patterns in a primary care population aged 55 years and over. Family Practice. 2015; 32(5):505-513. doi: 10.1093/fampra/cmv037.

Sinnige J, Braspenning JC, Schellevis FG, Hek K, Stirbu I, Westert GP, Korevaar JC. Inter-practice variation in polypharmacy prevalence amongst older patients in primary care. Pharmacoepidemiology and Drug Safety. 2016. doi: 10.1002/pds.4016.

Sinnige J, Korevaar JC, Van Lieshout J, Westert GP, Schellevis FG, Braspenning JC. Medication management strategy for older people with polypharmacy in general practice: a qualitative study on prescribing behaviour in primary care. British Journal of General Pracice. 2016: 66(649):e540-e551. doi: 10.3399/bjgp16X685681.

Sinnige J, Braspenning JC, Korevaar JC. Doktervariatie bij polyfarmacie. Huisarts & Wetenschap. 2016; 59(1):16.

Sinnige J, Braspenning JC, Schellevis FG, Hek K, Stirbu I, Westert GP, Korevaar JC. Bij iedere huisarts evenveel pillen? Interpraktijk-variatie in polyfarmacie*. Nederlands Tijdschrift voor Geneeskunde. 2017;161:D864.

Sinnige J, Braspenning JC, Schellevis FG, Westert GP, Korevaar JC. Clinical Medication Reviews in the general practice population: who and why? 2017. (submitted).

Holvast F, van Hattem BA, **Sinnige J**, Schellevis FG, Taxis K, Burger H, Verhaak PF. Late-life depression and the association with multimorbidity and polypharmacy – a cross-sectional study. Family Practice. 2017. Doi: 10.1093/fampra/cmx018.

Heins M, Kloek C, Francke A, **Sinnige J**, Swinkels I, Korevaar J, de Jong J. Naar een toekomstbestendige nazorg bij kanker: is er ruimte voor een grotere rol van de eerste lijn? 2016. Utrecht: NIVEL. ISBN: 9789461223920.

Dankwoord

DANKWOORD

Het proefschrift is af, wat een mijlpaal! Ik kan nu wel bekennen dat, toen ik solliciteerde voor de functie, het voor mij helemaal niet duidelijk was dat het om een promotietraject ging. Ik dacht dat ze op zoek waren naar een junior onderzoeker óf een promovenda. Doe mij die junior onderzoekersfunctie maar, dacht ik voordat ik aan het sollicitatiegesprek begon. Gaandeweg het gesprek werd het mij steeds duidelijker dat ik niet kon kiezen uit het één of het ander, het ging toch echt om een volledig PhD traject. Ik ben ontzettend blij dat ik de kans kreeg om dit traject te doorlopen, al was het niet altijd gemakkelijk. Elk promotietraject heeft zijn uitdagingen, en het mijne bestond uit het feit dat er alleen een startpunt was; multimorbiditeit in de huisartsenpraktijk. Er was geen onderzoeksvoorstel, het ging niet om een randomised controlled trial waar je duidelijk na een aantal jaar je effecten kunt meten, analyseren en daarover kan rapporteren. Het promotietraject had geen duidelijk eindpunt. Dit vond ik lastig. Zo moesten er soms beslissingen genomen worden over de weg die we zouden inslaan. Laat het nemen van beslissingen nou niet mijn allersterkste eigenschap zijn. Ik heb het gelukkig ontzettend getroffen met mijn promotieteam. De eindstreep is gehaald, en dat was niet gelukt zonder steun van verschillende personen.

Allereerst gaat er veel dank uit naar mijn promotoren en copromotoren. Vier in totaal maar liefst. Gert en François, ik was in het begin van mijn traject best wel onder de indruk (lees: nerveus) wanneer wij overleg hadden. Gert, als hoofd van IQ Healthcare, en François als expert op het gebied van multimorbiditeit. En natuurlijk beiden professoren. Onze gesprekken vielen gelukkig alles mee en ik ben jullie ontzettend dankbaar voor jullie deskundigheid, opbouwende kritiek en feedback. Jozé en Joke -als wij samen overleg hadden stond dit altijd als *Overleg 3Js* in mijn agenda-, ook met jullie als copromotoren heb ik het getroffen. Joke, vooral de eerste drie jaar spraken wij elkaar geregeld. Je deur stond letterlijk altijd voor mij open en je hebt mij in dit traject echt op weg geholpen met je duidelijke antwoorden en adviezen. Dankjewel daarvoor. Jozé, in mijn jaar bij IQ Healthcare hadden wij structureel overleg en ik was altijd heel blij met je waardevolle feedback. Onze overleggen gingen niet alleen over werk. Dankjewel dat je mij ook gesteund hebt op persoonlijk vlak, als ik weer eens worstelde met mijn onzekere ik en voor je interesse in mijn privé leven.

Mijn dank gaat ook uit naar alle anderen die hebben bijgedragen aan de artikelen in dit proefschrift. Irina Stirbu, je hebt mij wegwijs gemaakt in 'LINH', en nam altijd de tijd om mijn vragen te beantwoorden. Karin Hek, ik heb mij met jou gestort op de medicatie-data van NIVEL Zorgregistraties, de SFK, en ook letterlijk in de HIS'sen van huisartsen. Het was leerzaam en gelukkig ook erg gezellig om met jou op stap te gaan voor de interviews. Met je kritische blik hebben we de data van de verschillende databases in een mooi artikel kunnen verwerken. Peter Spreeuwenberg, wat heb ik vaak in jouw deuropening gestaan.

Je hebt mij geholpen met het artikel over de 'multimorbidity patterns', maar ook voor het 'polypharmacy' artikel heb jij veel vragen van mij beantwoord. En weer opnieuw, als ik de gang van de derde etage had doorkruist, weer aan mij bureau zat en toch nog steeds niet alles begreep. Je nam hier altijd de tijd voor en daar ben ik erg blij mee geweest. Jan van Lieshout, als huisarts en onderzoeker hebben wij samen de case-vignetten in elkaar gezet. Bedankt voor alle feedback. Zonder jou waren de vignetten nooit zo realistisch en complex geworden en had ik niet zulke interessante focusgroepen gehouden.
Bedankt Rodrigo voor alle hulp rondom NIVEL Zorgregistraties, bedankt Ernie Wentink en Elsbeth de Leeuw-Stravers voor jullie inzet bij de praktische organisatie van de interviews. Bedankt Alfons Olde Loohuis, als voorzitter bij de focusgroepen heb jij de huisartsen goed bij de les gehouden. Bedankt Tim Schoenmakers, via jou heb ik verschillende heel interessante gesprekken met apothekers gevoerd over medicatiebeoordelingen. En natuurlijk bedankt Jolanda van Haren, voor je hulp bij het daadwerkelijk maken van het boekje.

Prof. dr. M.G.M. Olde Rikkert, prof. dr. W.J.J. Assendelft en prof. dr. R.J. van Marum, jullie vormden samen de manuscriptcommissie die dit proefschrift heeft beoordeeld en heeft goedgekeurd. Hartelijk dank hiervoor.

Ik heb enkele maanden bij IQ Healthcare op de flexkamer in de kelder gezeten. Hoewel het voor mij altijd wel een verrassing was wie ik elke week zou aantreffen, werd ik er altijd hartelijk ontvangen. Ook schoof ik graag aan bij de lunches daar, bedankt daarvoor. Maar bijna mijn gehele promotietraject heb ik doorgebracht op kamer 3.07 van het NIVEL. Tessa, Lisa en ik vormden daar denk ik toch wel de 'harde kern'. Alle drie in hetzelfde jaar gestart, en inmiddels alle drie bezig met (het afronden van) ons proefschrift. Gedurende mijn loopbaan bij het NIVEL zijn er nog verschillende andere kamergenootjes geweest, en altijd was het gezellig. Dank daarvoor Karien, Karin, Linda en Maaike. Het laatste jaar deelden wij een bureau, Anne-Karien, maar gelukkig betekende dit niet dat wij elkaar nooit zagen. Ik vond het erg gezellig samen met jou in 3.07, je was altijd in voor een praatje, en je had altijd wel wat beleeft in het weekend om over te kletsen. Lisa en Tessa, wat was ik blij met jullie als roomies. Beiden harde werkers en gefocust. Ik kon altijd met jullie sparren over het één of ander, even zeuren als het niet ging zoals ik wilde, of mijn ei kwijt als ik ergens mee zat. Gelukkig ging het niet altijd over werk. Lisa, in 2015 waren wij alle twee zwanger. Dat schept toch een band. Jouw dochter was net een paar maanden eerder geboren, en als kersverse moeder heb ik je altijd om advies kunnen vragen :-). Tessa, beiden fanatieke volleybalsters. Iedere week deelden we een wedstrijdverslag. We zouden goed in een team passen, jij als lange middenaanvalster en ik als snelle setupster. Met mijn verdediging staan jullie naast mij, Lisa en Tessa, bedankt dat jullie mijn paranimfen willen zijn!

Het leven bestaat gelukkig niet alleen uit werk. Bedankt meiden, duinrellers, en de dames van mijn volleybalteam voor alle prettige afleiding! Bedankt Marrie en Peter, jullie zijn geweldige schoonouders, ik voel mij altijd welkom bij jullie! Bedankt Derk, Irene, Rob en Melanie, wat een leuk stel schoonbroertjes en zusjes samen! Bedankt mam en pap, dat jullie mij altijd steunen en achter mijn beslissingen staan. Ruben, wat een gekke grote broer heb ik, bedankt daarvoor!

Lieve Kay, jij bent mijn kleine vriendje, en wat ben ik ongelooflijk blij met jou! Ik kijk uit naar alle avonturen die wij samen gaan beleven. Lieve Frank, bedankt voor alles! Jij zou er niet aan moeten denken om zo in het middelpunt te staan. Toch ben jij mijn middelpunt, zonder jou had ik het niet gekund en zou het leven niet zo mooi zijn.

About the author

ABOUT THE AUTHOR

Judith Sinnige was born on October 3th 1986 in Beverwijk, the Netherlands. She grew up in Heemskerk and in 2005 she completed her Gymnasium at the Kennemer College in Beverwijk (formerly known as Augustinus College). That same year she started her study Health Sciences at the VU University in Amsterdam and obtained her Bachelor of Science degree in 2008. In 2009, she obtained her master degree in Health Sciences (specialization: prevention and public health) at the VU University in Amsterdam. As part of the master program, she completed a research internship at the Institute of Health Sciences (VU University Amsterdam) where she studied the quality of implementation intentions for condom use. During the bachelor and master program, Judith was active for Salus, the study association for Health Sciences. From 2009-2012 she worked as a junior epidemiologist at two Public Health Services (in Dutch: GGD) in the province Noord-Holland. In July 2012, Judith started her PhD project of which the results are described in this PhD thesis. The research project was a collaboration between IQ Healthcare, Radboudumc in Nijmegen and the Netherlands Institute of Health Services Research (NIVEL) in Utrecht. Judith is currently working at Nictiz, the national competence center for standardization and eHealth.

PHD PORTFOLIO

Name PhD student: E.J. (Judith) Sinnige **Department:** IQ healthcare **Graduate School:** Radboud Institute for Health Sciences	**PhD period:** 15-07-2012 – 15-11-2016 **Promotor(s):** Prof. dr. GP Westert, Prof. dr. FG Schellevis **Co-promotor(s):** Dr. JC Braspenning, Dr. JC Korevaar

TRAINING ACTIVITIES	Year(s)	ECTS
a) Courses & Workshops		
- Literature search in Pubmed (NIVEL)	2012	0.1
- STATA introduction course (NIVEL)	2012	0.3
- Applied statistics with STATA (NIVEL)	2013	2.0
- Academic writing in English (BABEL)	2013	2.1
- NCEBP Introduction course (NCEBP)	2013	1.0
- Quality system NIVEL and performing intern audits (NIVEL)	2013	0.2
- Presenting your research in Dutch (Radboud University)	2013	1.5
- Presenting in English (BABEL)	2014	1.5
- STATA advanced course (NIVEL)	2014	0.3
- Multilevel Analysis (EpidM)	2014	1.5
- eBROK course (NFU)	2015	1.5
- Scientific journalism (Radboud University)	2015	3.0
- Career Guidance (Radboud University)	2016	1.5
b) Seminars & lectures		
- Dag van het Advies thema 'Implementatie van Kwaliteitsstandaarden', Zorginstituut	2014	0.1
- SFK Raad van Toezicht: oral presentation	2015	0.5
- NIVEL Zorgregistraties huisartsendag: oral presentation	2015	0.5
c) Symposia & congresses		
- Congres 'Multimorbiditeit: onze uitdaging'	2013	0.25
- NHG Wetenschapsdag LUMC (Leiden)	2013	0.25
- CARE RIHS Symposium: laptop presentation	2014	0.5
- NHG Wetenschapsdag UMCG (Groningen): oral presentation	2014	0.5
- NHG Wetenschapsdag Erasmus MC (Rotterdam): poster presentation with short oral presentation	2015	0.5
- European General Practice Research Network (EGPRN) conference Edirne (Turkey): oral presentation	2015	0.75
- NHG Wetenschapsdag AMC (Amsterdam): poster presentation with short oral presentation	2016	0.5
- WONCA Europe Copenhagen (Denmark): two oral presentations	2016	1.25
d) Other		
- Themagebiedoverleg Huisartsenzorg (NIVEL) (including several oral presentations)	2012-2016	1.5
- Kennisgroep transparantie (IQ Healthcare)	2012-2015	0.5
- Reviewing scientific papers for multiple journals	2015, 2016	0.3
TOTAL		**24.4**